Early Tumor Drug Pharmacokinetics Is Influenced by Tumor Perfusion but not Plasma Drug Exposure

Azeem Saleem and Pat M. Price

Abstract

**Purpose:** Pharmacokinetic parameters derived from plasma sampling are used as a surrogate of tumor pharmacokinetics. However, pharmacokinetics-modulating strategies do not always result in increased therapeutic efficacy. Nonsurrogacy of plasma kinetics may be due to tissue-specific factors such as tumor perfusion.

**Experimental Design:** To assess the impact of tumor perfusion and plasma drug exposure on tumor pharmacokinetics, positron emission tomography studies were done with oxygen-15 radiolabeled water in 12 patients, with 6 patients undergoing positron emission tomography studies with carbon-11 radiolabeled 1-(2-(dimethylamino)ethyl)acridine-4-carboxamide and the other 6 with fluorine-18 radiolabeled 5-fluorouracil.

**Results:** We found that tumor blood flow (mL blood/mL tissue/minute) was significantly correlated to early tumor radiotracer uptake between 4 and 6 minutes [standard uptake value (SUV)4.6; \( \rho = 0.79; P = 0.002 \)], tumor radiotracer exposure over 10 minutes [area under the time-activity curve (AUC)0-10; predominantly parent drug; \( \rho = 0.86; P < 0.001 \)], and tumor radiotracer exposure over 60 minutes (AUC0-60; predominantly radiolabeled metabolites; \( \rho = 0.80; P = 0.002 \)). Similarly, fractional volume of distribution of radiolabeled water in tumor \( (V_d) \) was significantly correlated with SUV4.6 (\( \rho = 0.80; P = 0.002 \)), AUC0-1.10 (\( \rho = 0.85; P < 0.001 \)), and AUC0-6.00 (\( \rho = 0.66; P = 0.02 \)). In contrast, no correlation was observed between plasma drug or total radiotracer exposure over 60 minutes and tumor drug uptake or exposure. Tumor blood flow was significantly correlated to \( V_d \) (\( \rho = 0.69; P = 0.014 \)), underlying the interdependence of tumor perfusion and \( V_d \).

**Conclusions:** Tumor perfusion is a key factor that influences tumor drug uptake/exposure. Tumor vasculature-targeting strategies may thus result in improved tumor drug exposure and therefore drug efficacy.

Clinical anticancer drug development begins with dose-escalating phase I clinical trials of the investigational agent and leads to phase III/IV trials, before a drug is accepted for clinical use. Although the primary objective of phase I clinical trials is to establish the recommended phase II dose and assess drug toxicity, most phase I trials also aim to evaluate drug pharmacology (pharmacokinetics and pharmacodynamics). Clinical pharmacology plays an ever increasing role in drug development and can potentially aid in dose-schedule selection, therapy response monitoring, and the development of targeted strategies. In addition to providing information on drug pharmacology, plasma pharmacokinetic parameters such as plasma drug exposure [area under the concentration-time curve (AUC)], peak plasma concentrations, and steady-state plasma concentrations have been used as pharmacodynamic markers of drug efficacy and utilized to optimize therapy with anticancer agents such as methotrexate (1) and carboplatin (2). However, the limited utility of plasma pharmacokinetic parameters to select and optimize anticancer therapy so far may be due to the nontranslation of parameters obtained from plasma samples as surrogates of tumor pharmacokinetics.

Functional imaging modalities such as positron emission tomography (PET) and magnetic resonance imaging allow noninvasive evaluation of tissue and tumor drug uptake and exposure in vivo, thus providing invaluable tissue pharmacokinetic data (3, 4). We have previously reported from PET studies of radiolabeled anticancer agents that tumor drug exposure is several-fold less than in most normal tissues (4, 5). This differential in drug exposure may be a result of several factors that may be either drug-specific (drug pharmacokinetics, ionization status, lipophilicity) or tissue-specific (tissue vasculature/ permeability, drug efflux mechanisms, saturation in uptake). Tumor vasculature is widely recognized as a potential therapeutic target in order to improve tumor drug delivery and clinical efficacy (6). However, in vivo clinical
In this article, we report our findings obtained from PET perfusion studies with oxygen-15 radiolabeled water and tumor drug uptake and exposure of two radiolabeled drugs: N-[2-(dimethylamino)ethyl]acridine-4-carboxamide (DACA), which is lipophilic (7), and 5-fluorouracil (5-FU), a hydrophilic (dimethylamino)ethyl]acridine-4-carboxamide (DACA), which is lipophilic (7), and 5-fluorouracil (5-FU), a hydrophilic.

In addition, we also evaluated the influence of tumor perfusion on tumor drug pharmacokinetics after in vivo administration of [11C]DACA or 5-[18F]FU; cold drug doses prior to or during PET scanning, tissue drug pharmacokinetic parameters were not confounded by changes in tissue pharmacokinetics due to saturable kinetics and potential drug-related tissue pharmacodynamic (vascular) changes.

All PET scans were done on the ECAT931 scanner as described previously (4, 5, 9). Briefly, a perfusion PET scan was done after the inhalation of [15O] CO2 or the infusion of [15O]H2O. The short half-life of oxygen-15 (2 min), allowed drug pharmacokinetic scans to be done soon thereafter, after a short time interval. Arterial blood sampling was done throughout the scan duration to obtain plasma time-radioactivity curves. Metabolite analysis was done as described previously at predetermined times, during the drug scan duration (4, 5, 9). From this the total radioactivity and the parent drug radioactivity ([11C]DACA or 5-[18F]FU) was calculated. Metabolite analysis was done at 5, 10, 20, 40, and 60 min in 3 patients (4) and at 5, 10, 20, 45, and 60 min for the other 3 patients (9) with [11C]DACA-PET scans, and at 2, 5, 10, 30, and 60 min with 5-[18F]FU-PET scans (5), as described previously.

**Data analysis.** Tumor perfusion was calculated using the methods described previously to obtain perfusion parameters (5). Briefly, kinetic modeling was used to fit the plasma arterial input function derived from calibrated continuous arterial plasma radioactivity data and the tumor time-activity curve (output) to obtain perfusion parameters: flow (ml blood/ml tissue/min) and the partition coefficient of water or the volume of distribution of radiolabeled water (units attributed include ml blood per ml tissue, ml blood per cc tissue or ratio - unitless). The volume of distribution (Vd) is defined as the volume of blood that contains the same quantity of radioactivity as unit ml (or cc) of tissue at equilibrium (10). This definition is equivalent to the ratio of tissue concentration of the tracer (kBq/ml) to the blood concentration (kBq/ml) at steady state, and for water can be thought of as the fractional volume of tissue into which water can pass (i.e., the volume of the tissue excluding lipid deposits such as fat and membranes).

Three tumor pharmacokinetic parameters — standardized uptake value from 4 to 6 min (SUV$_{4-6}$) reflective of peak drug uptake, area under the time-activity curve (AUC) from 0 to 10 min (AUC$_{0-10}$), and AUC from 0 to 60 min (AUC$_{0-60}$) — were used to quantify the extent of tumor vasculature on tumor drug pharmacokinetics.
radiolabeled drug uptake and exposure. It should be noted that the radiolabeled tumor uptake was representative of the total activity, i.e. radiolabeled drug and its radiolabeled metabolites and not the radiolabeled parent drug alone. Tumor uptake (SUV4-6) and exposure (AUC0-10 and AUC0-60) parameters were normalized for injected radioactivity and patient body surface areas to obtain parameters with units of m²/mL and m²/mL × sec, respectively.

Plasma exposure to the parent drug and total radiotracer from 0 to 10 min (AUC0-10) and 0 to 60 min (AUC0-60) to signify early and total plasma exposure, respectively, were calculated from the plasma parent and plasma total radiotracer time-activity curves (TAC), respectively, using the trapezoidal method. Plasma parent drug exposure (Pl_Parent AUC0-10 and Pl_Parent AUC0-60) and total radiotracer exposure (Pl_Total AUC0-10 and Pl_Total AUC0-60) were similarly normalized as tissue data for injected radioactivity and patient body surface area to obtain parametric values in units of m²/mL × sec for comparison with the tumor pharmacokinetic data.

Statistical analysis. Correlations among tumor pharmacokinetic parameters (SUV4-6, AUC0-10, and AUC0-60), tumor perfusion parameters (flow and Vd), and plasma exposure parameters (Pl_Total AUC0-10, Pl_Parent AUC0-10, Pl_Total AUC0-60, and Pl_Parent AUC0-60) were sought using Spearman’s correlation analysis. A P value of < 0.05 was considered significant.

Results

Patients. All 12 patients included had both perfusion and drug kinetic PET imaging of tumors. For the DACA scans,

Table 2. Tumor pharmacokinetic, tumor perfusion, and plasma pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Pt. no.</th>
<th>AUC0-60 (m²/mL × s)</th>
<th>AUC0-10 (m²/mL × s)</th>
<th>SUV4-6 × 10³ (m²/mL)</th>
<th>Flow (mL/mL/min)</th>
<th>Vd</th>
<th>Pl_Total AUC0-60 (m²/mL × sec)</th>
<th>Pl_Parent AUC0-60 (m²/mL × sec)</th>
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<td>0.024</td>
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<td>0.018</td>
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<td>0.456</td>
<td>0.085</td>
<td>0.021</td>
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<td>0.024</td>
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<td>0.216</td>
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<td>5*</td>
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<td>0.086</td>
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<tr>
<td>6</td>
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<td>0.020</td>
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<td>0.395</td>
<td>0.085</td>
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<td>7*</td>
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<td>0.033</td>
<td>0.178</td>
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<td>0.200</td>
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<tr>
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<tr>
<td>9*</td>
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<td>0.191</td>
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<tr>
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<td>0.554</td>
<td>0.144</td>
<td>0.037</td>
</tr>
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<td>11*</td>
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<td>0.150</td>
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<td>0.641</td>
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<tr>
<td>12</td>
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<td>0.233</td>
<td>0.794</td>
<td>0.205</td>
<td>0.062</td>
</tr>
</tbody>
</table>

NOTE: Patients 1 to 6 received [¹¹C]DACA, whereas patients 7 to 12 received 5-[¹⁸F]-5-FU.

*More than one tumor region imaged. Tumor parameters were averaged in these instances.
6 patients with 9 tumor metastases were included (Table 1). Similarly, 6 patients with 9 metastases were included in the 5-FU study. A list of patients included, diagnosis, and amount of drug and radioactivity injected are given in Table 1. Tumor uptake (SUV_{4-6}) and exposure (AUC_{0-10}, AUC_{0-60}) to radio-labeled drug and metabolites and tumor perfusion parameters (flow and V_d) were available in all patients. All plasma samples were taken at the proposed times in all patients, except in one patient (patient 5), who did not have the 15-minute plasma sample.

**Plasma drug exposure.** Plasma TACs showed a rapid decrease in plasma radioactivity of total tracer (radio-labeled parent drug and metabolites) and the radio-labeled parent drug after tracer doses of both 5-[^{18}F]FU and [^{11}C]DACA. TAC profiles showed a rapid clearance of radioactivity from plasma with both radio-tracers, especially of the parent radio-labeled drug (Fig. 1A and B), underlining the extent of metabolite contribution with both these agents. In contrast to [^{11}C]DACA, plasma 5-[^{18}F]FU levels were not observed 30 minutes after the injection of tracer doses of 5-[^{18}F]FU, as reported previously (11). In keeping with the observed plasma profile, Pl_Parent AUC_{0-60} was less than Pl_Total AUC_{0-60}. A strong correlation was observed between Pl_Total AUC_{0-10} and Pl_Parent AUC_{0-10} (ρ = 0.88; P < 0.001) and Pl_Total AUC_{0-60} and Pl_Parent AUC_{0-60} (ρ = 0.99; P < 0.001). Similarly, early and late plasma exposure parameters were significantly correlated (Pl_Total AUC_{0-10} and Pl_Total AUC_{0-60}, ρ = 0.96; P < 0.001 and Pl_Parent AUC_{0-10} and Pl_Parent AUC_{0-60}, ρ = 0.92; P < 0.001). A summary of the plasma AUC for parent and total tracer for 5-[^{18}F]FU and [^{11}C]DACA is given in Table 2.

**Tumor drug uptake and exposure.** Tumor uptake and exposure to radioactivity varied among tumor types in contrast to similar TAC profiles seen in normal tissues, as reported previously (4, 5, 9). Tumor TACs for all the patients included in this analysis are shown in Fig. 1C, and representative hepatic TACs for two patients (patient 3 for DACA and patient 7 for 5-FU), showing the hepatic metabolism of both DACA and 5-FU, are also illustrated for comparison with tumor TACs in Fig. 1D. Early tumor uptake (SUV_{4-6}) was significantly correlated to tumor radiotracer (parent drug and metabolites) exposure over 10 min (AUC_{0-10}, ρ = 0.96; P < 0.001) and was also significantly correlated to tumor radiotracer (parent drug and metabolites) exposure over 60 minutes (AUC_{0-60}, ρ = 0.88; P < 0.001). Early tumor radiotracer exposure (AUC_{0-10}) is reflective of tumor exposure to radiolabeled parent, which is the predominant entity in plasma at early time points (Fig. 1A and B), whereas tumor radiotracer exposure over 60 minutes (AUC_{0-60}) is predominantly due to metabolites for tracer doses of both agents studied, which are extensively metabolized. AUC_{0-10} and AUC_{0-60} were also correlated (ρ = 0.81; P = 0.002). Tumor uptake and exposure parameters were averaged, in which more than one tumor region was sampled in the same patient. Tumor radiotracer uptake parameters are summarized in Table 2.

**Tumor perfusion.** Tumor flow and V_d parameters for the patients sampled are given in Table 2. In instances in which more than one tumor region was sampled in the same patient (four patients), the perfusion parameters were averaged, as in previous studies (12). Tumor flow varied considerably between patients, with a mean (SE) flow of 0.224 (0.066) ml blood/ml.

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**Figure 2.** Scatter plot (A) illustrating the significant relationship between tumor perfusion parameters flow and V_d (ρ = 0.69; P = 0.014). Scatter plots (B) and (C) illustrate the lack of relationship between tumor drug exposure over 60 min (AUC_{0-60}) with plasma exposure to total plasma radiotracer over 60 min (ρ = 0.04; P = 0.9) and plasma exposure to parent drug over 60 min (ρ = -0.13; P = 0.7), respectively. In D the lack of relationship between plasma exposure to parent drug over 10 min and tumor exposure over 10 min (AUC_{0-60}) is illustrated (ρ = 0.24; P = 0.47).
tissue/minute. In contrast, the variability in $V_d$ of water was less between patients, with a mean (SE) of 0.537 (0.065). A significant correlation was observed between the two tumor perfusion parameters, flow and $V_d$ ($\rho = 0.69; P = 0.014$; Fig. 2A).

Relationship of tumor drug uptake/exposure to plasma exposure and tumor perfusion. Correlation scatter plots for tumor exposure over 60 minutes, with plasma exposure to activity associated with the total radiotracer (parent and metabolites) and parent drug (DACA or 5-FU) over 60 minutes, are illustrated in Fig. 2B and C, respectively. Plasma exposure to total radiotracer over 60 minutes (Pl_Total AUC<sub>0-60</sub>) did not correlate to radiotracer tumor SUV<sub>4-6</sub> ($\rho = 0.25; P = 0.44$), tumor AUC<sub>0-10</sub> ($\rho = 0.32; P = 0.32$), or tumor AUC<sub>0-60</sub> ($\rho = 0.04; P = 0.9$). Similarly, a lack of relationship was observed for plasma exposure to radiolabeled parent drug over 60 minutes (Pl_Parent AUC<sub>0-60</sub>) with radiotracer tumor SUV<sub>4-6</sub> ($\rho = 0.09; P = 0.78$), tumor AUC<sub>0-10</sub> ($\rho = 0.2; P = 0.54$), or tumor AUC<sub>0-60</sub> ($\rho = -0.13; P = 0.7$). Additionally, we observed a lack of relationship between plasma exposure to total radiotracer over 10 minutes (Pl_Total AUC<sub>0-10</sub>) and radiotracer tumor SUV<sub>4-6</sub> ($\rho = 0.18; P = 0.59$), tumor AUC<sub>0-10</sub> ($\rho = 0.22; P = 0.51$), or tumor AUC<sub>0-60</sub> ($\rho = -0.03; P = 0.93$). No corelationship was also observed between Pl_Parent AUC<sub>0-10</sub> and radiotracer tumor SUV<sub>4-6</sub> ($\rho = 0.2; P = 0.56$), tumor AUC<sub>0-10</sub> ($\rho = 0.24; P = 0.47$; Fig. 2D), or tumor AUC<sub>0-60</sub> ($\rho = 0.09; P = 0.98$).

In contrast to lack of correlation between plasma parameters and tumor drug kinetics, early radiotracer uptake (SUV<sub>4-6</sub>) was significantly correlated to tumor blood flow ($\rho = 0.79; P = 0.002$; Fig. 3A). Similarly, tumor perfusion was significantly correlated to radiotracer tumor AUC<sub>0-10</sub> ($\rho = 0.86; P < 0.001$) and AUC<sub>0-60</sub> ($\rho = 0.80; P = 0.002$; Fig. 3B). The volume of distribution of radiolabeled water was also significantly related to SUV<sub>4-6</sub> ($\rho = 0.80; P = 0.002$; Fig. 3C), AUC<sub>0-10</sub> ($\rho = 0.85; P < 0.001$), and AUC<sub>0-60</sub> ($\rho = 0.66; P = 0.02$; Fig. 3D).

**Discussion**

This article describes the impact of tumor perfusion parameters with reference to plasma pharmacokinetic parameters in influencing in vivo tumor uptake and exposure of two anticancer agents. The conclusions made in this analysis are based on PET perfusion studies with radiolabeled water, tissue pharmacokinetic studies with radiolabeled anticancer agents, and supplementary plasma pharmacokinetic data obtained during PET scanning in the same patients with cancer. This was made possible by the dynamic nature of PET data acquisition with short half-lived positron emitters, the highly sensitive nature of PET, and analysis of plasma data in the same patient during a single scanning session.

We have clearly shown that neither early tumor uptake nor tumor exposure to the parent drug and metabolites (total radiotracer) is related to plasma exposure to parent drug or metabolites. This PET study confirms similar findings of a lack of relationship between plasma and tumor drug levels with other anticancer agents shown using noninvasive (3, 13) or invasive methods (14). Despite our inability to make a generalization based on the limited data, it would be reasonable to conclude that this lack of surrogacy between plasma and tumor kinetics may partly explain the limited clinical activity
observed for a number of anticancer agents, in spite of tumoricidal plasma pharmacokinetics. It is therefore important that tissue-specific pharmacodynamic information be accrued wherever possible, in addition to plasma pharmacokinetics during the early phases of anticancer drug development (15).

In contrast, we observed that both tumor blood flow and $V_{d}$ of radiolabeled water played a significant role in influencing tumor drug uptake and exposure to the total radiotracer. Although we have previously reported on the impact of tumor flow on tumor drug exposure and the influence of tumor perfusion on changes in drug uptake (4, 12, 16), this is the first report that has additionally evaluated the influence of tumor $V_{d}$ of radiolabeled water and plasma pharmacokinetics on tumor drug uptake and exposure in vivo clinically. In addition to a significant relationship between tumor flow and tumor exposure with both $5\text{-}[^{18}\text{F}]\text{FU}$ and $[^{11}\text{C}]\text{DACA}$ (4, 12, 16), we also found that $V_{d}$ of radiolabeled water significantly correlated with tumor drug uptake/exposure. These findings not only confirm the importance of tumor blood flow but also highlight the role of exchangeable fractional $V_{d}$ on drug uptake. The significant positive correlation observed in our study between tumor blood flow and $V_{d}$ highlights an interdependence of flow and fractional $V_{d}$ in tumors and underlies the importance of water exchangeable tumor tissue on tumor blood flow.

However, the relationship between flow and $V_{d}$ in normal tissues was not evaluated in this analysis. Our group is also assessing the relationship between the perfusion parameters and the effects of vascular targeting agents on perfusion in normal tissue and tumors. Although not reported by Wilson et al. in their article evaluating flow and $V_{d}$ in normal breast and breast tumors (17), analysis of the individual patient data provided in their article suggests that flow and $V_{d}$ of water are related in tumors ($p = 0.55; P = 0.012$) but not in normal breast ($p = 0.29; P = 0.27$). Therefore, the relationship between flow and $V_{d}$ seen in tumors is due to physiologic changes and not to parameter estimation artefacts.

Our study evaluated the importance of two perfusion parameters: blood flow and $V_{d}$ of water in tumors. Although both these parameters indicate tissue perfusion characteristics, they signify different features of tissue perfusion (Fig. 4). Whereas tumor flow provides a quantitative indication of the volume of blood perfused per unit volume of tumor, $V_{d}$ signifies the exchangeable tumor volume at steady state or the volume of tumor with which radiolabeled water from plasma equilibrates. As a measure of the concentration of radiolabeled water in a fraction of tissue, $V_{d}$ is dependent on the amount of viable tissue per unit volume measured, fatty content (17), extent of tissue necrosis, and fibrosis. Although we do not have a direct measure of tumor interstitial fluid pressure, we hypothesize (Fig. 4) that $V_{d}$ may also represent and reflect changes in interstitial fluid pressure, which is considered an important barrier to the effective delivery of molecules into tumor tissue (18). This raises interesting possibilities in the sequencing of tumor interstitial fluid pressure-reducing agents when combining with other cytotoxic agents, vascular disrupting agents, or radiotherapy (19–21).

Despite drug lipophilicity being an important determinant of tissue drug uptake, the significant relationship observed between tumor perfusion and drug uptake of both lipophilic (DACA; ref. 7) and hydrophilic (5-FU; ref. 8) agents (and their metabolites) in our study underscores the influence of tumor perfusion on tumor drug delivery. It is therefore important to take into consideration the poor tumor vascular supply that may limit tumor drug uptake with all anticancer agents, irrespective of their lipophilicity. On the basis of direct influence of perfusion on early tumor drug uptake (SUV$_{4\sim6}$) and exposure (AUC$_{0\sim60}$), it is likely that tumor perfusion may play an especially influential role on therapy where anticancer drug efficacy based on preclinical models is dependent on tumor peak plasma concentration levels that usually occur during the early period of bolus infusions. However, it is not possible to extrapolate that similar improvements in perfusion would lead to improvements in tumor exposure, as the tumor exposure data in our analysis are limited to 60 minutes (AUC$_{0\sim60}$) only. Moreover, in our study with tracer quantities of drugs, the predominant plasma contribution at latter time points is mainly due to radiolabeled metabolites unlike early uptake (SUV$_{4\sim6}$), when radioactivity is predominantly associated with the parent drug. We point out that all patients included in this analysis were administered tracer amount of drugs (microdoses) and not therapeutic concentrations. It is likely that the relationship between perfusion parameters and tumor drug uptake may not hold true at higher drug concentrations. It is not possible, however, to speculate on this relationship from data obtained in this analysis.
In conclusion, we have shown that tumor perfusion is more important than plasma drug exposure in determining early tumor drug uptake and exposure. The importance of tumor perfusion justifies the need for adapting anticancer treatment strategies that target tumor vasculature. If tumor vasculature is targeted judiciously with a clear understanding of biological and chronological tumor perfusion patterns, there is tremendous potential to improve the therapeutic benefit.

References


Disclosure of Potential Conflicts of Interest

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