Magnetic Resonance Pharmacoangiography to Detect and Predict Chemotherapy Delivery to Solid Tumors

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ABSTRACT

Detection and prediction of drug delivery to the tumor interstitium are of critical importance in cancer chemotherapy. Prediction of drug delivery derived from standard pharmacokinetic models is frequently inadequate because of the complex nature of tumor blood flow and the microenvironment. Although drug concentrations can be directly sampled with microdialysis or in biopsy samples, we currently lack methods capable of detecting and/or predicting drug delivery to tumors noninvasively. In this study, we describe a novel magnetic resonance (MR) technique to directly detect the drug, and we present the correlation between delivery of drug and the delivery of MR contrast agents to the tumor. Experiments were performed with tumor xenografts in severe combined immunodeficient mice. Three-dimensional maps of the drug distribution within the tumors were obtained with 13C spectroscopic MR imaging with a spatial resolution of 2 × 2 × 2 mm, using signals of the 13C-labeled anticancer agent phenylacetate. Three-dimensional maps of uptake of gadolinium-diethylenetriaminepentaacetic acid (GdDTPA) contrast agent were obtained for the same tumors using dynamic MR imaging. Experimental data were analyzed for correlation between delivery of the drug and the contrast. Histological analysis was performed for excised tumors. Experimental data demonstrated a significant spatial correlation (r = 0.59 with P < 0.001) between the parameter representing delivery of the contrast to tumor interstitium, determined from the kinetic curves of GdDTPA, and integral tissue drug concentrations for two different tumor models. The method is designed to probe extravasation of the drug molecules from the bloodstream into the tumor interstitium. Although therapeutic efficiency of the drug will also depend upon drug retention in the tumor and the ability of the molecules to cross cellular membranes, inefficient drug transfer from plasma to tissue can be a major impediment in achieving effective tumor chemotherapy. The results of this study demonstrate that the uptake kinetics of a low molecular weight MR contrast agent can be used to predict delivery of drug molecules of similar size to the interstitium of solid tumors.

INTRODUCTION

The effectiveness of chemotherapy of tumors can be severely impaired by limited delivery of the drug to the tumor because of low and heterogeneous blood flow (1) and for large molecules because of elevated intratumoral pressure (2). Thus, drugs with high in vitro efficiency often fail to exhibit sufficient activity against solid tumors in vivo (3) because of inefficient transfer of drug from plasma to the tumor interstitium (4). Drug pharmacokinetics within the tumor environment depend upon a combination of physiological and drug-related parameters such as degree of tumor vascularization, efficiency of drug delivery by blood flow, and drug stability during transport to and within the tumor physiological environment. Drug transport across the cellular membrane depends on the hydrophobic properties of the drug and, for small charged molecules, on pH gradients across the membrane (5).

Direct measurements of intratumoral drug concentrations are difficult to perform in vivo, and traditional pharmacokinetic models cannot account for the complexities of the tumor microenvironment and blood flow. Although tissue drug concentrations within the tumor can be sampled with a microdialysis system (6), noninvasive alternatives for detection or prediction of drug delivery to tumors are yet to be developed. PET imaging of radiolabeled drugs can provide a possible solution to the problem but is limited by the low spatial resolution typical for PET scans and the high costs involved in synthesis of labeled drugs and imaging studies (7, 8). MR spectroscopy is the only truly noninvasive technique, other than PET, which can detect a compound of interest in the tissue. With recent advances in MR techniques, we can now noninvasively measure the distribution of certain anticancer agents within a solid tumor and simultaneously characterize, with contrast enhanced MRI, the vascular parameters upon which drug delivery is dependent. We used this approach to test the ability of paramagnetic contrast agent-enhanced MRI to predict the delivery of drugs to solid tumors, using parameters of tumor microcirculation derived from the MRI data for experimental animal tumor models.

An inherent problem of MR spectroscopy is its low signal/noise ratio of detection, in comparison with nuclear medicine methods. However, recent results, obtained by our group and others, show that certain anticancer agents administered at clinically relevant doses can be detected in solid tumors in vivo by MR spectroscopy (1, 9, 10). These drug pharmacokinetic studies have been performed with 19F, 13C, and 1H MR spectroscopy and imaging. 19F MR spectroscopy in vivo experiments demonstrated that 5-fluorouracil and its major metabolites and catabolites can be detected in animal and clinical experiments (11–13). Proton MR spectroscopy was performed for iproplatin using double quantum coherence selection for editing drug signals from the overlapping lipid resonance (10, 14). Labeling of drug molecules with a 13C isotope is an important alternative that enables their MR detection in vivo (15) with minimal modification of the chemical and biological properties of the drug. Several technical approaches can significantly increase the sensitivity of detection of 13C, making the method feasible for in vivo application (15–17).

Most MR studies directly detecting chemotherapeutic agents in tumors have been performed with agents that can be administered at high doses to allow detection by MR (1). These agents are, therefore, by necessity less toxic and mostly consist of agents that are categorized as cytostatic or preventive. Differentiating agents (18) and specific and nonspecific nonsteroidal anti-inflammatory drugs that have recently attracted significant attention as alternatives for prevention and/or treatment of various cancers (19) fall under these categories. However, most of the clinically used cytotoxic drugs are delivered at doses where tissue concentrations are well below MR detection limits of ∼1 mM. Of these, 5-fluorouracil is the only chemotherapeutic agent that has been extensively studied in patients using MR (11–13). For such low concentration drugs, it may still be possible to predict drug pharmacokinetics and spatial distribution with 2

Received 9/13/00; accepted 1/26/01.

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The study was supported by American Cancer Society Institutional Research Grant (to D. A.), and in part by NIH ROI CA73850.

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2 The abbreviations used are: PET, positron emission tomography; MRI, magnetic resonance imaging; MRSI, magnetic resonance spectroscopic imaging; CA, contrast agent; GdDTPA, gadolinium-diethylenetriaminepentaacetic acid; NOE, nuclear Overhauser effect; PA, phenylacetate.
high temporal and spatial resolution from the pharmacokinetics and spatial distribution of a paramagnetic MR CA using dynamic MRI (20–22). The constraints for such an approach would be to ensure that the chemotherapeutic agent and the paramagnetic MR CA have similar transport parameters, such as water/lipid solubility, molecular radius, and macromolecular binding properties, as well as the same route of delivery. In this study, we have demonstrated the feasibility of such an approach by comparing the intratumoral pharmacokinetics of the $^{13}$C-labeled differentiating agent PA, measured directly by three-dimensional MRSI, with the delivery of the low molecular weight contrast agent GdDTPA, measured with dynamic $T_1$ MRI and analyzed using Larson’s model for contrast tissue uptake (23). These studies were performed for two different tumor models with significantly different proliferation rates and doubling times. The experimental results show a significant spatial correlation between the uptake and distribution of the contrast agent and the drug within the tumor interstitium. Such an approach is easily translated to the clinical setting by using MRI of GdDTPA and may be of significant use in determining the delivery of a chemotherapeutic agent to a tumor during the course of chemotherapy.

**MATERIALS AND METHODS**

**Animals.** Male and female severe combined immunodeficient mice (4–6 weeks of age) were used for experiments with prostate and breast tumor xenografts, respectively. All animal experiments were performed in accordance with institutional guidelines. For the MR studies, mice were anesthetized with a mixture of ketamine/acepromazine (40 mg/kg and 4 mg/kg, respectively, in 0.9% NaCl solution) administered i.p. At the end of the study, animals were sacrificed, and the tumors were excised for histology.

**Tumors.** The estrogen-independent human breast cancer cells, MDA-MB-435, were inoculated into the upper thoracic mammary fat pad of female mice (10⁶ cells/0.05 ml of HBSS) and grown for a period of ~5 weeks. Androgen-independent rat prostate cancer cells, MatLyLu, were inoculated in the flank of male mice (10⁶ cells/0.05 ml of HBSS) and allowed to grow for a period of 10–12 days. The average tumor volume used in this study was ~500 mm³. MDA-MB-435 tumors reached this size within 30–35 days of inoculation, whereas MatLyLu tumors reached this size within 12 days.

**Chemicals.** $^{13}$C-labeled PA ([2-13C]PA 99%; Cambridge Isotopes, Inc.) was dissolved in 0.9% NaCl solution with the pH adjusted to 7.2 with NaOH. The final concentration of the filtered injection solution was adjusted to 0.3% mm. Low molecular weight GdDTPA CA (Magn vest; Berlex Laboratory, Wayne, NJ) was used for all of the contrast-enhanced dynamic MRI studies.

**MR Experiments.** All MR studies were performed with a GE Omega-400 instrument equipped with shielded imaging gradients (52-mm room bore diameter) and a home made probe consisting of a double-tuned $^1$H/$^13$C detection coil (diameter, 13 mm; Ref. 15). Anesthetized animals were placed in the probe, to facilitate coregistration of data sets. A schematic diagram of the pulse sequences used in the study are shown in Fig. 1.

**Data Processing.** After completion of MR experiments, data processing was performed of line on a Silicon Graphics Octane workstation using IDL software (Research Systems, Inc., Boulder, CO).

**Contrast Uptake.** Tissue concentrations of the paramagnetic CA GdDTPA $C(t)$ were determined from the multislice $T_1$ maps obtained before and for 9 min after administration of the contrast using the equation $C(t) = \frac{C_m}{T_1 - T_1^{-1}}$, where fast exchange conditions are assumed. Concentration versus time curves were analyzed using the equation for Larson’s model (23):

$$C(t) = k_{in}^{PS} \int_0^t C_m(\tau) \times \exp(k_{out}^{PS}(\tau-t))/v_e d\tau$$

(A)

where $k_{in}^{PS}$ is the influx volume transfer constant [min⁻¹], $k_{out}^{PS}$ is the “outflow constant,” and $v_e$ is the extravascular extracellular space per unit volume of the tissue. In a simplified model of contrast uptake (20) the volume transfer constants are assumed equal, $k_{in}^{PS} = k_{out}^{PS}$. In tumors where delivery of the CA can be flow limited, this simple relation may not hold; also, parameter $v_e$ is not known. Therefore, we used a two-parameter fit of the equation (1) and determined two independent parameters $k_{in}$ and $k_{out}$ proportional to the volume transfer constants $k_{in}^{PS}$ and $k_{out}^{PS}$, respectively. In the rest of the paper, parameters $k_1$ and $k_2$ will be used as indices of contrast uptake and clearance. The arterial input function $C_{a(t)}$ used in the model was independently measured in vitro using samples of arterial blood from the catheterized carotid artery and averaged for three animals. Three-dimensional maps for the parameter $k_2$ were generated on a pixel by pixel basis for the entire data set and were interpolated to a 16 × 16 × 16 data set corresponding to a spatial cube with a side length of 16 mm.

**Drug Delivery.** Three-dimensional MRSI data were filtered with a Gaussian window in the spatial domains and an exponential window in the time domain and Fourier transformed using absolute value calculation. The integral of the [2-13C]PA peak at 45 ppm was calculated for each voxel of the three-dimensional data set, and the final three-dimensional image of integral drug concentrations was interpolated to the 16 × 16 × 16 matrix corresponding to the 16 × 16 × 16-mm cube. The drug uptake data set was registered as a 3D image using the MIBI acquisition block.

**CSI Experiment:** The three-dimensional MRSI data were filtered with a Gaussian window in the spatial domains and an exponential window in the time domain and Fourier transformed using absolute value calculation. The integral of the [2-13C]PA peak at 45 ppm was calculated for each voxel of the three-dimensional data set, and the final three-dimensional image of integral drug concentrations was interpolated to the 16 × 16 × 16 matrix corresponding to the 16 × 16 × 16-mm cube. The drug uptake data set was registered as a 3D image using the MIBI acquisition block.

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Fig. 1. A saturation recovery Turbo-FLASH fast imaging. The saturation block is repeated three times to completely suppress initial magnetization. Phase encoding is rearranged to shift the central phase encoding steps with low gradient values to the beginning of the acquisition block. B, three-dimensional spectroscopic imaging $^{13}$C pulse sequence with NOE signal enhancement and BB proton decoupling during acquisition. Flip angle of the radiofrequency pulse is optimized according to the Ernst’s principle.
with the data set for the contrast uptake parameter $k_t$ for all animals, using translation in three-dimensional space. Because MR data sets were acquired without disturbing the position of the animal, the maximum translation length was limited to $± 2$ data points in the $X$, $Y$, or $Z$ direction.

**Histology.** After completing MR studies, the animals were sacrificed, and tumors were excised, fixed in 10% buffered formalin at pH 7.4, dehydrated, and embedded in paraffin blocks. Up to 10 $5\mu$m sections were cut to provide a uniform coverage of the whole tumor. All sections were deparaffinized and stained with H&E to determine the fraction of viable and necrotic cells. Optical images were digitized at high resolution with a CCD camera (Sanyo, 1/3") attached to an Olympus microscope.

**Statistical Analysis.** Correlation between drug delivery and contrast uptake data sets was determined with Pearson’s correlation. The significance of correlation was evaluated using a two-tailed significance test. Association between delivery of the drug and the CA was assessed with linear regression analysis using Student $t$ test with ($n - 2$) degrees of freedom for the regression parameter $b$.

**RESULTS**

Typical results for the curve fitting of the CA to Eq. A in a single voxel of a three-dimensional image are shown in Fig. 2. The arterial input curve of the CA used in the convolution integral is also shown on the plot. The best fit was produced with a Powell nonparametric routine implemented in the IDL language. The appearance of the $[2-13C]$PA peak in the nonlocalized spectra of the tumor, during the course of drug infusion, is shown in Fig. 3. Broadband decoupled NOE $13C$ spectra were acquired with 128 scans/spectrum with a 1-s repetition delay. Reconstructed images of the contrast uptake parameter $k_t$ and integral drug concentration for a MatLyLu and an MDA-MB-435 tumor are shown in Fig. 4 for eight slices obtained with identical spatial localization. Spatial registration of the proton MR images corresponding to the contrast uptake and $13C$ spectroscopic images for drug delivery was performed using an interactive three-dimensional volume rendering routine using small adjustments of linear offsets. A color presentation of three-dimensional data sets of contrast uptake and drug concentration within the MatLyLu tumor is shown in Fig. 5 using the green channel for the CA and the red channel for drug. On the composite image, yellow regions correspond to areas where high contrast uptake spatially correlates with high drug concentrations. A high degree of spatial correlation between tissue concentration of the drug and contrast uptake is evident in the image.

Correlation analysis of the spatial distribution of contrast and drug uptake was performed for 6 MatLyLu and 4 MDA-MB-435 tumors. Individual results are presented in Table 1 with averaged values of the Spearman’s correlation coefficient of $R_{MLL} = 0.62$ for MatLyLu tumors and $R_{MDA} = 0.55$ for MDA-MB-435 tumors. Both results are statistically significant with $P = 0.001$. Data sets for both drug and contrast uptake contain significant number of zero points, which can produce erroneously high correlation when taken into account. Therefore, zero points were excluded from the correlation analysis of the experimental data.

The significant correlation between parameters of contrast and drug uptake allowed us to analyze the experimental data using linear regression analysis. Results for the individual tumors are summarized in Table 1. Averaged values of regression coefficients for the two tumor models studied are: $b_{MLL} = 156 ± 20$ and $b_{MDA} = 89 ± 13$, measured in relative units, where the errors represent the SE. Scatter plots of the data and the corresponding linear regression line are shown in Fig. 6 for representative data sets for a MatLyLu tumor and an MDA-MB-435 tumor. As for the correlation analysis, zero points were excluded from the linear regression analysis. A comparison of contrast and drug uptake maps with a histological section obtained from this region for an MDA-MB-435 tumor is shown in Fig. 7. Both contrast and drug uptake were significantly reduced in the central region of the tumor, which corresponded to a region of central necrosis in the histological section.

**DISCUSSION**

The data demonstrated a significant correlation between the delivery of low molecular weight MR CA and the integral concentration of a small molecular weight drug, irrespective of the origin, inoculation site, and growth rate of the tumor. Tissue uptake of the CA was assessed by the parameter $k_n$, which is a complex function of the vascular characteristics of the tissue determined as the index of GdDTPA uptake. For fast water exchange across the vascular wall typical for tumors, the parameter $k_n$ is proportional to $E \cdot F = F (1 - \exp ((PSI/F)))$, where $F [\text{ml/g min}]$ is the capillary blood flow per unit mass of tissue, $P [\text{cm/min}]$ and $S [\text{cm}^2/\text{g}]$ are permeability and surface area per gram of tissue, respectively, and $E$ is the extraction fraction (the fraction of tracer that leaves the blood and enters the tissue during one pass of blood through the capillary bed; Ref. 20). Generally, for a given plasma concentration, drug delivery to target tissue and its clearance from the interstitium are primarily dependent on tissue perfusion and the micropermeability of the vasculature to the
drug molecules (28). Interstitial pressure gradients that may exist within the solid tumors are of lesser importance for the delivery of low molecular weight substances, because the transport of molecules from the capillaries to the interstitium is mainly by diffusion, for compounds with molecular weight $M_r < 2000$ (2, 29). Thus, for a chemically stable drug with a defined arterial input function, the accumulation of drug in the tissue will be highly dependent upon the product of regional blood flow rate $F$ and the extraction fraction of the drug $E$, which is directly proportional to the index of contrast uptake $k_1$. The pharmacokinetics at later time points or retention of the drug in the tissue may differ from that of GdDTPA because of differences in the volume of distribution because drug molecules can traverse the cellular membrane, whereas GdDTPA is an extracellular agent. Differences in different clearance rates and possible metabolic conversion of drug molecules may also lead to differences in pharmacokinetics between GdDTPA and the drug molecules at later time points. The contrast uptake index $k_1$ relates to the initial uptake rate of the CA and therefore does not depend on its clearance $k_2$. Parameter $k_1$ is a measure of the transport of small molecules across the vascular wall into the tumor interstitium. It can be measured with high spatial resolution using contrast enhanced dynamic MRI and can therefore be used as a “pharmacoangiographic” marker to predict the delivery of drug molecules.

To prove the feasibility of this approach, in our study the uptake of the CA was compared directly with MR measurements of tissue concentrations of [2$^\text{13}$C]PA drug detected with high sensitivity in the same tumor. PA belongs to a group of aromatic fatty acid compounds known to induce differentiation in a wide range of human tumors (18, 30–32). The mechanisms by which the agent reduces cell proliferation and induces re-expression of genes silenced in cancer are still not clear. Some of the often synergistic mechanisms proposed include: (a) depletion of serum glutamine by conjugating PA (33); (b) inhibition of the mevalonate pathway which interferes with synthesis of sterols and isoprenoids; (c) inhibition of isoprenylation of ras and related proteins (34); (d) inhibition of histone deacetylase (35) and DNA methylation (36); and (e) activation of human peroxisome proliferator-activated receptors (37, 38). Phase I clinical trials revealed that doses of PA $\geq$ 20 g/day (250 mg/kg) are well tolerated by the patients (39). The drug concentration used in our studies with mice (650 mg/kg) was well tolerated, and the animals completely recovered after the experiments, without signs of neurosuppression. The concentration used provided sufficient MR signal to enable in vivo drug detection with a spatial resolution of 8 mm$^3$.

For all animal studies, contrast uptake measurements were performed before $^{13}$C CSI of the drug. $^{13}$C spectroscopic imaging studies were commenced within 15 min of completing GdDTPA-enhanced MRI, without altering the position of the animal and/or tumor in the

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**Table 1** Pearson’s correlation coefficients and linear regression parameters for drug/contrast delivery for the individual tumors

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>Correlation R$^a$</th>
<th>Regression b</th>
</tr>
</thead>
<tbody>
<tr>
<td>MatLyLu</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0.62</td>
<td>173 ± 6</td>
</tr>
<tr>
<td>II</td>
<td>0.56</td>
<td>106 ± 4</td>
</tr>
<tr>
<td>III</td>
<td>0.60</td>
<td>90 ± 3</td>
</tr>
<tr>
<td>IV</td>
<td>0.49</td>
<td>157 ± 7</td>
</tr>
<tr>
<td>V</td>
<td>0.78</td>
<td>177 ± 4</td>
</tr>
<tr>
<td>VI</td>
<td>0.66</td>
<td>68 ± 3</td>
</tr>
<tr>
<td>MDA-MB-435</td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>0.55</td>
<td>94 ± 4</td>
</tr>
<tr>
<td>II</td>
<td>0.51</td>
<td>51 ± 2.2</td>
</tr>
<tr>
<td>III</td>
<td>0.61</td>
<td>89 ± 3</td>
</tr>
<tr>
<td>IV</td>
<td>0.54</td>
<td>46 ± 2</td>
</tr>
</tbody>
</table>

$^a$ All values represent significant correlation with $P \leq 0.001$ ($n \geq 40$).
radiofrequency coil, to ensure complete registration of the data sets. Our reasons for this particular sequence of experiments were: (a) no interference of residual GdDTPA with $^{13}$C detection of signals of the drug was observed in the experiments; and (b) i.v. administration of high dose of the drug could cause changes in tumor perfusion affecting delivery of the CA to the tumor. Contrast uptake was obtained from quantitative pixel-by-pixel $T_1$ maps of the tumor after administration of the CA. In comparison with steady-state type experiments ($T_1$ weighted imaging), this approach provides a linear dependence of the parameter on the tissue concentration of the contrast agent, and the method is not sensitive to changes in $T_2$ and $T_2^*$ caused by the contrast agent. The trade-off of this technique is the longer acquisition time and lower spatial resolution. To improve the temporal resolution of the method, we developed a saturation recovery Turbo-FLASH sequence for fast acquisition of three-dimensional quantitative $T_1$ maps, which is extensively used in our laboratory for the study of experimental tumors (40). By using saturation recovery, the long relaxation delays between consecutive single-shot acquisitions are not required. Furthermore, $T_1$ maps measured with nonselective saturation of the entire tumor are not prone to fresh blood inflow artifacts. Reduced spatial resolution of a single-shot $T_1$ imaging is not relevant for our studies because it still remains significantly higher than the spatial resolution of $^{13}$C spectroscopic imaging.

Two tumor lines with significantly different growth rates and different origins were chosen for these experiments. MDA-MB-435, a hormone-independent, highly metastatic human breast cancer line with relatively slow proliferation rate, was inoculated orthotopically in the mammary fat pad of female mice. On the other hand, MatLyLu, a rapidly growing aggressive rat prostate cancer cell line, was inoculated s.c. Despite these widely different factors, which can result in a significantly different tumor microenvironment, the regression analysis did not reveal statistically significant changes between delivery of the drug and the index of contrast uptake for both tumor lines. A positive intercept of the regression line with the $Y$ axis (drug uptake), corresponding to a measurable drug delivery to the region of the tumor with negligibly low contrast uptake, was observed in most of the model tumors. This result can be rationalized from the facts that: (a) the low spatial resolution of $^{13}$C spectroscopic imaging of drug distribution is prone to significant volume averaging effects (41); and (b) the drug uptake maps were recorded with time averaging for a period of ~40 min. During this time, the diffusion of the drug molecules within the tumor interstitium may give rise to local drug concentrations within areas of otherwise low delivery. As seen from Fig. 6, this contribution is limited to not more than 25% of the maximum drug integral intensity within the tumor.

Histological analyses of regions of low drug and contrast agent concentration demonstrated necrosis in these areas, supporting the possibility that the delivery of even low molecular weight chemotherapeutic agents may be nonuniform as well as limited in solid tumors.

In conclusion, in this study we have demonstrated, for the first time, that the delivery of a low molecular weight drug to a solid tumor can be approximated by measuring the delivery of a similarly sized MR CA. The dependence was established using PA, which can be administered at a high clinical dose and therefore is directly detectable with MR, allowing correlation analyses for individual voxels within the tumor. The close agreement of regression analysis for two widely different tumor models suggests that the uptake and distribution of an MRI CA, such as GdDTPA, can be used to quantitatively predict intratumoral drug concentration and distribution. The limitations of the technique are that: (a) the drug should obey the same tracer characteristics as the contrast agent (GdDTPA in this case); and (b) the method can only predict efficiency of drug delivery to the inter-

Fig. 7. Maps of contrast uptake (A), drug uptake (B), and H&E stained histological section (C) of the slice from an MDA-MB-435 tumor with a region of central necrosis.
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stium of solid tumors and not the drug retention in the tissue. The latter is determined by combination of unique properties of drug molecules such as lipophilicity and possible metabolic modification of the chemical structure of drug molecules. The application of such an approach can be extended even further by developing surrogate non-toxic, GdDTPA-based MRI contrast agents that “mimic” the size and lipophilicity of chemotherapeutic agents used in a particular treatment regimen. The ability to predictively visualize drug delivery to regions of the tumor will play a significant role in evaluating the effectiveness of various chemotherapeutic agents currently in use, because it can be used to rule out uncertainties in treatment outcome attributable to failure of the drug to reach the tumor. Such an approach may also significantly alleviate normal tissue toxicities associated with chemotherapy, because it will be possible to determine whether poor response is attributable to poor delivery rather than resistance of the cells to the drug, in which case it would be more appropriate to improve delivery rather than escalate the dose.

ACKNOWLEDGMENTS

We thank G. Cromwell for transplanting the tumors.

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*Cancer Res* 2001;61:3039-3044.

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