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Dynamic Contrast Enhanced-Magnetic Resonance Imaging as a Pharmacodynamic Biomarker for Pazopanib in Metastatic Renal Carcinoma

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Abstract

Introduction/Background—Traditional imaging assessment criteria may not correlate well with clinical benefit from vascular endothelial growth factor pathway-directed therapy in metastatic renal cancer. Preclinical data suggest tumor growth is preceded by a rise in K^{trans} , a parameter derived from dynamic contrast enhanced (DCE)-MRI that reflects vascular permeability. We thus hypothesized that K^{trans} may be a predictive biomarker for pazopanib.

Patients and Methods—Patients with metastatic renal cancer were treated with pazopanib at 800 mg oral daily until disease progression. MRI of the abdomen and pelvis with a DCE-MRI sequence was obtained at baseline and every 8 weeks.

Results—Seventy-three DCE-MRIs were completed and 66 were technically assessable. Of the 17 patients with at least one post-baseline DCE-MRI, 16 (94%) had a decline in K^{trans} . Changes in K^{trans} compared to baseline after 1, 8, 16, and 24 weeks were -49% , -65% , -63% , and -53% , respectively ($P = 0.0052$, RM ANOVA). The median K^{trans} nadir occurred at 8 weeks. The median progression free survival (PFS) was 32.1 weeks. PFS was longer in patients with a higher baseline K^{trans} values ($P = 0.036$, log-rank). Baseline K^{trans} did not reach significance in a Cox-proportional hazard model including clinical prognostic index and prior treatments ($P = 0.083$).

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Conclusion—We demonstrate that K^{trans} is a pharmacodynamic biomarker for pazopanib therapy in metastatic renal cancer. Due to the small sample size, the predictive capacity of K^{trans} recovery could not be assessed, but baseline K^{trans} correlated with progression free survival.

Keywords

Renal cancer; DCE-MRI; VEGF receptor tyrosine kinase; K^{trans} ; progression

INTRODUCTION

Clear cell renal cancer is characterized by inactivation of the von Hippel-Lindau (VHL) pathway, which leads to upregulation of the HIF2 α transcription factor and vascular endothelial growth factor (VEGF).¹ This process results in angiogenesis that is necessary for growth, invasion, and metastases. Modern antineoplastic therapies have exploited this dependency by targeting the VEGF pathway. Pazopanib is one such FDA approved agent.^{2, 3} While generally efficacious, the duration of benefit with VEGF pathway inhibitors, such as pazopanib, is variable. Furthermore, traditional imaging assessment criteria may not correlate well with clinical outcome since these drugs often result in growth inhibition, as opposed to direct cytotoxicity.⁴ Thus, it remains difficult to determine whether a patient continues to derive benefit from treatment at clinical re-assessment with each cycle. Given that these agents can have significant toxicities impacting quality of life, identification and validation of novel biomarkers in this space is critical.

Quantitative and semi-quantitative parameters derived from dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) have been identified as biomarkers for VEGF pathway-directed agents.⁴⁻⁸ Some studies have also demonstrated predictive and prognostic value for DCE-MRI-based biomarkers.^{6, 7} K^{trans} is one parameter that reflects perfusion rate and capillary permeability. Studies in renal cancer have demonstrated that it declines an average of 30% upon treatment with VEGF targeted therapy, making it a potentially important pharmacodynamic biomarker.^{6, 7, 9} The initial change in K^{trans} is dose dependent, but has not been shown to correlate with time to progression in prior studies. There remains limited clinical data on longitudinal assessment of K^{trans} during VEGF pathway directed therapy. Pre-clinical animal models strongly suggest that changes in blood flow and perfusion, as assessed by K^{trans} , precede tumor growth.^{10, 11} We thus hypothesized that recovery of K^{trans} is predictive of progression in metastatic renal cancer patients treated with pazopanib. In order to address this question, we conducted a clinical trial with serial assessments of K^{trans} during treatment with pazopanib for patients with metastatic renal cancer.

PATIENTS AND METHODS

Patients

Patients with histologically confirmed metastatic clear cell renal cancer without prior pazopanib therapy were eligible. Other requirements included measurable disease with at least one lesion in the abdomen or pelvis ≥ 20 mm on MRI or CT scan, WHO performance status 0 to 2, and normal organ function defined as GFR > 30 mL/min, AST/ALT $\leq 2.5 \times$

upper limit of normal, and total bilirubin ≤ 1.5 upper limit of normal. Exclusion criteria included patients with central nervous system metastases, uncontrolled hypertension (defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg), pregnancy, and anti-cancer therapy within 14 days of study enrollment.

Study Design

Patients were treated with pazopanib at 800 mg oral daily without food (GlaxoSmithKline) on 28-day cycles until disease progression as measured using Response Evaluation Criteria in Solid Tumors. Standard MRI of the abdomen and pelvis was obtained at baseline and every 8 weeks ± 1 week for tumor burden assessment. An investigational dynamic contrast enhanced (DCE) sequence was added to the standard image acquisition sequences to calculate K^{trans} and associated physiologic parameters. An additional investigational DCE-MRI imaging procedure was conducted 1 week ± 1 day after initiation of drug therapy. The protocol included a total of 5 DCE-MRI procedures per patient. Toxicity monitoring using National Cancer Institute Common Toxicity Criteria version 3.0 was performed and dose modifications made for grade 3 or 4 toxicities. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by the University of Chicago's institutional review board.

MRI Acquisition

MR images were acquired on a 1.5T Philips Achieva scanner (Philips Healthcare, Andover, MA), using an 8-channel torso local coil. Gadobenate dimeglumine (Multihance, Bracco, Cranbury Township, NJ) was used as the contrast agent, at standard dose of 0.1 mmol/kg (0.2 mL/kg). For patients with compromised kidney function ($GFR < 60$ mL/min/1.73m²), one half of the standard dose was administered.

The standard clinical part of the MRI scan covered the whole abdomen and included axial and coronal non-fat suppressed single-shot FSE sequences (TR/TE = 1800/80 ms, flip angle = 90°), an axial fat suppressed T2-weighted sequence (TR/TE = 1800/80 ms, flip angle = 90°), an axial diffusion-weighted MRI (fat suppressed spin-echo EPI, TR/TE = 7155/67 ms, flip angle = 90°, $b = 800$ s/mm²), and an axial breath-hold T1-weighted fat suppressed sequence (TR/TE = 4.07/1.98 ms, flip angle = 10°), acquired before and 3 minutes post-contrast administration (delayed phase).

Research sequences were acquired in a 36 mm thick axial slab centered over the largest cross-section of a selected metastatic lesion in an area with minimal MRI, especially motion related, artifacts. Limited coverage was necessary to insure high temporal resolution with adequate signal to noise ratios. The location of the slab was determined by the clinical radiologist (A.O.) based on previous CT or MRI imaging, and was selected at the level of largest lesion cross-section. The location of the slab was kept constant in subsequent scans, relative to the spine. An axial non-fat suppressed T1-weighted dual-echo DCE-MRI 3D sequence (TR/TE1/TE2 = 8.5/3.0/6.0 ms, flip angle = 10°, in-plane resolution = 2 mm, field-of-view = 380 \times 356 mm, slice thickness = 3 mm both acquired and reconstructed, number of slices = 12, partial Fourier factors = 0.7 and 0.85 in the Y and Z directions, SENSE acceleration factor = 1.2 in the anterior/posterior direction, time resolution = 9.8 s) was

acquired for 16 minutes, with 10 dynamic phases acquired prior to contrast agent injection, and the rest acquired post-contrast. The clinical delayed phase whole abdomen T1-weighted sequence was nested into the research DCE-MRI sequence at 3 minutes post-contrast administration, which did not affect the gain or other pre-scan parameters.

Contrast Agent Concentration Calculation

Contrast agent concentration was calculated as an average over regions of interest (ROIs) outlined over the lesion, muscle, and adipose tissue and over the aorta cross-section in slices in which they were visible. The edge slices (first and last 3 slices) had reduced flip angles due to the non-ideal slab profile, and were not used for calculation. Concentration versus time curves for lesion, muscle, and arterial ROIs were calculated using the reference tissue method published earlier.¹² In short, the approximate inverse proportionality of signal to T1 in the short TR T1-weighted DCE-MRI sequence was utilized. Based on the tabulated value of native T1 in adipose tissue ($T1_{ref} = 288$ ms),¹³ and its average pre-contrast signal intensity $S_{ref}(0)$, the pre-contrast and post-contrast T1, and hence the contrast agent concentration as a function of time $C(t)$ in each ROI could be approximated using Eq. 1:

$$C(t) \approx \frac{1}{RT1_{ref}S_{ref}(0)} (S(t) - S(0)), \quad [1]$$

where $R = 5.6$ L/mmol/s (as obtained from the manufacturer data sheet) is the relaxivity of the contrast agent at 1.5T, and $S(0)$ and $S(t)$ are average signal in the ROI pre-contrast and as a function of time, respectively.

K^{trans} Calculation

Prior to further analysis, the $C(t)$ curves for tumor and muscle were smoothed via a fit to the 5-parameters empirical mathematical model (EMM), shown previously to provide excellent fits to the concentration uptake curves in tissues.¹⁴⁻¹⁶ Two compartment modeling¹⁷ was used to iteratively fit smoothed $C(t)$ curves to Eq 2:

$$\frac{dC(t)}{dt} = K^{trans} \cdot (C_p(t) - C(t)/v_e) \quad [2]$$

where K^{trans} is the volume transfer constant between the intravascular extracellular space and extravascular extracellular space (EES), v_e is the volume of EES per unit volume of tissue, and $C_p(t)$ is the arterial input function (AIF). The AIF was obtained as the contrast concentration curve from the arterial ROI for each patient, and was corrected for hematocrit by dividing the contrast agent concentration in the arterial ROI by (1- hematocrit), with hematocrit = 0.45, i.e., $C_p(t) = C_{arterial}(t)/(1-0.45)$.

Statistical Analysis

The primary study endpoint was to determine whether a rise in K^{trans} from nadir is predictive of subsequent tumor growth. Secondary endpoints included the association between changes in K^{trans} and pazopanib therapy. The pre-defined principal metric assessed, R , was the log ratio of K^{trans} at time t_i to the lowest K^{trans} among the first 2 (baseline or 1

week post therapy), a time-dependent covariate. The main analysis was to assess whether the time-dependent variable R had a significant impact on the hazard rate for disease progression in a Cox proportional hazards model also incorporating a baseline clinical prognostic index (good/intermediate/poor)^{18, 19} and prior VEGF pathway inhibitor therapy (yes/no) as covariates. We assumed that the median time to progression in this patient population is 8 months and that K^{trans} variability and change with therapy are similar to that seen in prior studies.⁹ Exploratory objectives included correlating baseline K^{trans} with progression free survival (PFS). Kaplan-Meier estimates and log-rank tests were computed to evaluate the association between changes in K^{trans} and PFS.

Trial size was based on prior data showing that the standard deviation in R from baseline to 4 weeks was approximately 0.40.⁹ A clinically meaningful effect was defined as a 50% increase in the hazard rate per one standard deviation increase in R. In order to have 80% power to detect an effect of this magnitude, a total of 48 events (disease progressions) were required. Assuming a median time to progression of 8 months, enrollment of 65 patients was planned.

RESULTS

Patient Characteristics and Feasibility of a Complex Biomarker Assessment

Due to poor accrual the study was closed after 20 patients were enrolled over the course of two years. Baseline characteristics of patients are summarized in Table 1. The median age was 63 (range, 50 – 82) and median number of prior therapies was two (range, 0 – 5). Fourteen (70%) patients were male. The median number of completed 28-day treatment cycles on study was four (range, 1 – 21). Eighteen (90%) patients underwent a baseline MRI with a calculable K^{trans} and were included in the analysis, while 17 patients (85%) also underwent at least one post-baseline MRI with a calculable K^{trans} . A median of 4 MRIs were obtained per patient.

Change in K^{trans} With Pazopanib Therapy

Of the 18 patients assessed, 73 DCE-MRIs were completed and 66 were technically assessable. The median baseline K^{trans} value was 0.472 min^{-1} , and the mean was 0.538 min^{-1} with a standard deviation of 0.339 min^{-1} . One patient did not have any assessable DCE-MRI studies after baseline due to poor uptake of contrast. Of the 17 patients with at least one post-baseline DCE-MRI, 16 (94%) had a decline in K^{trans} (Figure 1). Mean K^{trans} log ratios (\pm SD) compared to baseline after 1, 8, 16, and 24 weeks were $-0.680 (\pm 0.729)$, $-1.049 (\pm 0.634)$, $-0.998 (\pm 0.757)$, $-0.755 (\pm 0.952)$, respectively, corresponding to changes of -49% , -65% , -63% , and -53% ($P = 0.0052$, RM ANOVA). The recovery of mean K^{trans} at week 24 compared to the prior time point was not statistically significant ($P = 0.40$, Wilcoxon signed rank). Patients showed variability in the timing of K^{trans} decline and recovery as depicted in Figure 1B. At week 24 the K^{trans} values showed a broad range between 0.092 and 1.028 min^{-1} .

K^{trans} and Clinical Outcome

The median progression free survival (PFS) was 32.1 weeks. Kaplan-Meier analysis showed a significant difference in PFS in patients grouped dichotomously around the median baseline K^{trans} ($P = 0.036$, log-rank, Figure 2A). Patients with higher baseline values showed deeper reductions in K^{trans} after therapy (Figure 2B and 2C). The mean percent reduction in K^{trans} after one week of therapy was 61.8% in the group with higher baseline values versus 9.2% in the group with lower baseline values ($P = 0.017$, two-tailed t-test). Baseline K^{trans} did not reach significance in a Cox-proportional hazard model including clinical prognostic index and prior treatments ($P = 0.083$). With our accrued sample size, the primary study endpoint, whether K^{trans} recovery as a time-dependent covariate impacted hazard rate for disease progression, could not be assessed.

DISCUSSION

This prospective, non-randomized, imaging biomarker study demonstrates that K^{trans}, a quantitative parameter derived from DCE-MRI, is a pharmacodynamic biomarker for pazopanib therapy in metastatic renal cancer. To date, this is the first study to report the effect of pazopanib on a quantitative DCE-MRI-derived biomarker. The median K^{trans} nadir occurred eight weeks after initiating therapy, and a decline in K^{trans} was nearly universal, occurring in 94% of patients. Only a single patient did not show a decline, but data from only one follow up MRI for that patient was available at week one. It is likely that a decline was simply not captured due to the absence of assessment beyond one week. The declines in K^{trans} noted in our study were consistent with prior reports on other anti-angiogenic therapies in metastatic renal cancer.⁹ Interestingly, we observed variability among individual patients with some reaching their nadir at week one, while others continued to decline at the final 24-week assessment.

This study also assessed clinical outcomes in relation to K^{trans} values. It was hypothesized that recovery of K^{trans} would predict progression on pazopanib therapy. Indeed, there was a trend towards K^{trans} recovery by 24 weeks, which preceded the median progression free survival by 8 weeks. Unfortunately, due to the small sample size, the primary endpoint of K^{trans} recovery as a time-dependent covariate could not be assessed. Thus, the predictive capacity of K^{trans} recovery remains uncertain. It is notable that at week 24, the majority of patients still had K^{trans} values below their baseline. Thus, increasing the duration of serial DCE-MRI assessments beyond 24 weeks in future studies might capture more definitive K^{trans} recovery data in a greater fraction of patients. Baseline K^{trans} values did exhibit a significant association with progression free survival, an observation that is consistent with data reported in prior studies.⁹ We also found that higher baseline K^{trans} was associated with deeper declines at week 1. While there may be difficulty in utilizing absolute baseline K^{trans} levels between different populations, the percent reduction from baseline could be assessed at week one for an individual patient and might be consistent and reliable predictive measure to evaluate in future studies.

Despite not reaching its primary endpoint, this study was unique as the first to report serial DCE-MRI evaluations longitudinally over 24 weeks in renal cancer patients treated with VEGF therapy. It also demonstrated the feasibility of performing a complex biomarker study

using a multidisciplinary team of investigators. There remain challenges in the recruitment of patients for a study evaluating a novel biomarker for an FDA-approved therapy. Nonetheless, this study validated DCE-MRI-derived K^{trans} as a non-invasive, pharmacodynamic biomarker. Its baseline value correlates with progression free survival for pazopanib therapy in metastatic renal cancer, thus demonstrating its consistency across different anti-angiogenic drug therapies.

Clinical Practice Points

Dynamic contrast enhanced magnetic resonance imaging (DCE-MRI) is an emerging modality with potentially more sensitivity in assessing tumor growth compared to traditional imaging. K^{trans} is an important DCE-MRI-derived parameter that changes with alteration in tumor vascular permeability. Clinical studies have shown that in some cancers, such as renal carcinoma, K^{trans} declines shortly after initiation of vascular endothelial growth factor-targeted therapies. This study is the first to describe longitudinal serial assessments of K^{trans} in metastatic renal cancer patients treated with pazopanib. We report that K^{trans} consistently declined upon initiation of therapy, and that higher baseline K^{trans} correlated with longer progression-free survival. The data reported have implications for future studies using DCE-MRI as a pharmacodynamic biomarker. This technique may ultimately lead to more accurate tools to determine disease progression at an earlier time point than traditional imaging assessment, which could inform therapeutic changes at an earlier time point when treatment is no longer effective and possibly still causing toxicities impacting quality of life.

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Abbreviations

| | |
|----------------|--|
| DCE-MRI | Dynamic contrast enhanced magnetic resonance imaging |
| VEGF | Vascular endothelial growth factor |
| PFS | Progression-free survival |

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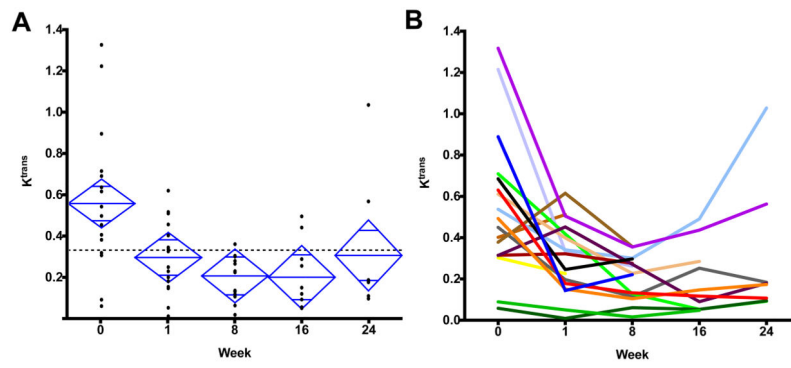


Figure 1. (A) Individual dynamic contrast magnetic resonance imaging (DCE-MRI) derived K^{trans} values (min⁻¹) plotted at each time point. The top and bottom of each diamond represent the 95% confidence interval for each group. (B) K^{trans} values (min⁻¹) plotted across each time point by individual patient. Each color represents an individual patient, with trend line shown over the course of the study.

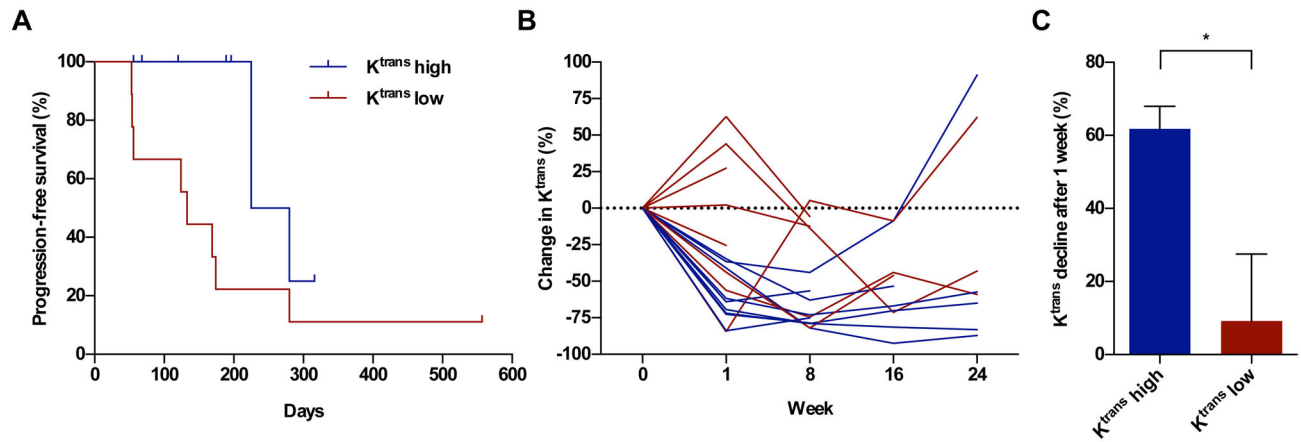


Figure 2.

(A). Kaplan-Meier estimates for progression-free survival (PFS) of patients with low and high baseline K^{trans} values (min^{-1}). The cut off value was defined as the median K^{trans} value, which was 0.472 min^{-1} . The PFS difference between groups was statistically significant ($P = 0.036$, log-rank). (B) Percent change in K^{trans} from baseline in individual patients colored by the groups of patients with high and low baseline K^{trans} values. (C) Bar graph comparing the depth of K^{trans} decline at one week for patients with high versus low baseline K^{trans} ($P = 0.017$, two-tailed t-test).

Table 1

Baseline Characteristics for Patients Enrolled on Trial

| Characteristic | No. of Patients (N = 20) |
|---------------------------|--------------------------|
| Sex | |
| Male | 6 |
| Female | 14 |
| Age | |
| Median | 63 |
| Range | 50–82 |
| Race/ethnicity | |
| White | 13 |
| African American | 2 |
| Hispanic | 2 |
| Not reported | 3 |
| Number of Prior Therapies | |
| 0 | 5 |
| 1 | 5 |
| 2 | 4 |
| 3 | 3 |
| 4 | 2 |
| 5 | 1 |
| Clinical Prognostic Index | |
| Good | 4 |
| Intermediate | 8 |
| Poor | 5 |
| Not available | 3 |