Evaluation of the role of DW-MRI in the assessment of tumor response to sunitinib in metastatic renal cell carcinoma.

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INTRODUCTION

Over recent years systemic treatment options for metastatic renal cell carcinoma (RCC) have evolved with a shift from traditional cytokine-based treatments such as interleukin-2, to targeted therapies, such as the tyrosine kinase inhibitor sunitinib. These targeted agents have shown significant improvements in progression-free survival and overall survival (1; 2).
The current standard imaging technique for evaluation of disease response is contrast-enhanced CT (CE-CT) in conjunction with response criteria such as RECIST 1.1. However, these techniques are not useful in the early prediction of which patients will respond to sunitinib. With these newer treatments, dynamic changes are occurring in the biological nature of the tumor which are not necessarily accompanied by a change in size. Therefore new imaging modalities need to be identified for response evaluation with the aim of tailoring management plans to an individual patient's tumor biology. Functional imaging techniques such as diffusion-weighted MRI (DW-MRI) have been proposed as potential biomarkers for the assessment of treatment response in other cancers.
The aim of our study was to evaluate this technique in the semi-quantitative assessment of response of primary RCC to neo-adjuvant treatment with sunitinib.

METHOD AND MATERIALS

The study protocol was approved by the local institutional review board and all patients gave permission for use of anonymised data for research.
All patients with newly diagnosed metastatic RCC referred to our tertiary referral uro-oncology centre were prospectively considered for inclusion in this phase II trial. Those fulfilling inclusion criteria underwent baseline staging with CE-CT and DW-MRI. Clear cell histology was confirmed on biopsy performed following the initial DW-MRI to avoid post-biopsy artefact. Patients were then treated with sunitinib and post-treatment imaging was performed following the third cycle. Nephrectomy was performed at least 2 weeks following the last dose of sunitinib in cycle 3. Following surgery, patients continued treatment with sunitinib until progression was documented.
Imaging protocol:
DW-MRI: All subjects were imaged using a 1.5 Tesla Philips Achieva MRI scanner (Philips Medical Systems, Best, The Netherlands) in conjunction with a 4-element torso phase array coil. DW-MRI images were obtained using a multi-slice single shot spin-echo type echo planar sequence under free breathing. In 3 patients the *b*-values used for the initial DW-MRI were 0 and 1000 s/mm^2 while in the remainder of the DW-MRI scans the *b*-values used were 0, 100, 200, 500, 750 and 1000 s/mm^2. *b*-values used during the study changed due to optimisation of protocols applied at our institution over the study period. In patients with only 2 *b*-values, both were used for calculation of the ADC map. Where 6 *b*-values were available, *b*=0 was excluded and the ADC map was calculated using the remaining 5 *b*-values (3).
CE-CT: All subjects underwent diagnostic quality CE-CT of the chest, abdomen and pelvis with triple phase imaging from the diaphragm to iliac crests.
Image analysis: Imaging data collected before and after treatment with sunitinib included RECIST 1.1 from CE-CT images and primary tumor volume, whole tumor mean ADC and histogram analysis from DW-MRI images. Pixel-by pixel ADC maps were generated using an in-house plug-in written for the open source software OsriX (4). Mean ADC was calculated over the entire volume of the tumor, care was taken to place the largest possible region of interest (ROI) on each axial slice within the lesion without contamination from adjacent normal tissues (fig 1). Histograms of the ADC values for the tumor were generated using Microsoft Excel.
Pathological data: The primary tumor subtype and grade were required for enrolment in the study. Following nephrectomy, the degree of tumor necrosis was assessed pathologically and expressed as a percentage of the tumor volume.

RESULTS

30 patients (23 male, 7 female) with metastatic clear cell RCC were recruited. 4 patients (2 male, 2 female) did not complete the study protocol for reasons other than progression. In the remaining 26 patients the mean age was 60.2 ± 10.3 years with a range of 38 to 78 years.
Pre-treatment biopsy showed G1 in 1 patient, G2 in 13 patients; G3 in 9 and G4 in 3 patients. Following nephrectomy, the degree of necrosis ranged from 5 to 70%.
On CE-CT, 16 patients showed overall stable disease by RECIST 1.1 while 8 patients progressed (6 patients died prior to completion of 3 cycles and did not have the second round of imaging) and 2 showed a partial response. The primary tumor volume reduced by greater than 30% in 8 patients and increased by more than 20% in 3 patients over the interval between scans.
The mean tumor ADC was 1.29±0.4x10^{-3}mm^2/s before treatment and 1.4±0.4x10^{-3}mm^2/s following treatment. 3 patients who showed an increase in primary tumor volume following 3 cycles also showed a decrease in mean tumor ADC. Patients with a decrease in tumor volume showed stability or an increase in ADC. Histogram analysis of ADC showed variable patterns. Patients with high degrees of necrosis at surgery showed a shift of the curve toward higher ADC values (fig 2).

CONCLUSION

This preliminary data is the first to investigate sequential functional imaging in RCC treated with sunitinib. Mean tumor ADC shows stability after treatment; however histogram analysis demonstrates subtle changes in the spread of values which may relate to outcome. These early results suggest that patients who respond to treatment show a shift in the mean tumor ADC histogram towards higher ADC values while poor responders remain stable or show a shift to lower values. Patients continue follow-up and updated outcome data will be included.

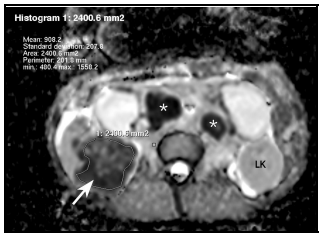

Fig 1. ROI placement: Care is taken to sample only tumor tissue in the right RCC (white arrow) without contamination from adjacent normal tissue. Involved retroperitoneal nodes (white stars) which return lower ADC values than the primary tumor are also noted. (LK = left kidney).

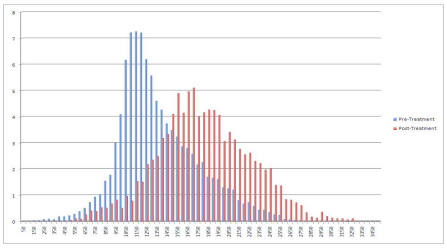

Fig 2. Histogram analysis: Primary tumor ADC values before (blue) and after (red) treatment with sunitinib. There is a shift towards higher ADC values and broadening of the curve following 3 cycles. This patient showed a 65% decrease in tumor volume and 33% increase in whole tumor mean ADC with treatment. At nephrectomy the specimen showed 50% necrosis.

References: (1) Motzer et al. J Clin Oncol 2009; 27:3584-3590. (2) Gore et al. Oncology 2006; 20:19-24. (3) Padhani et al. Neoplasia 2009; 11:102-125. (4) Rosset et al. J Digit Imaging. 2004; 17:205-216.