

Early therapy evaluation of sunitinib for gastrointestinal stromal tumors using quantitative perfusion and diffusion weighted magnetic resonance imaging: a pilot study

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Purpose: To assess the early response of gastrointestinal stromal tumors (GISTs) to sunitinib using diffusion-weighted (DW) and dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) in a clinical pilot study.

Materials and Methods: Five patients having newly diagnosed, biopsy-proven GISTs were accrued, and sunitinib was given at 37.5 mg as an oral daily dose for 6 weeks. MRI was performed prior to therapy initiation (baseline imaging) and at 2 and 6 weeks after therapy initiation. All subjects were examined on a single 3T clinical MR system using a torso phased array coil. Respiratory-gating DW single-shot echo-planar imaging (DW-SS-EPI) was performed with three b values of 0, 50, and 700 s/mm² in one direction with following parameters: repetition time/echo time (TR/TE) = 1586/55 ms, field of view (FOV) = 42×42 cm, number of excitation (NEX) = 4, thickness/gap = 7/1 mm, matrix size = 140/140 (interpolated to 288/288), and number of slices = 30-40. DCE-MR images were obtained by a breath-hold 3D fast field echo T1 weighted axial sequence with following parameters: TR/TE = 5/2.3 ms, FOV = 40×40 cm, NEX=1, thickness/gap = 6/0 mm, matrix = 192/154 (interpolated to 256×256), flip angle = 15°, and sensitivity encoding (SENSE) factor = 2. A total of 10 slices covering the central region of a tumor were obtained at each time (longitudinal FOV: 6 cm), and a total of 91-120 images per slice were continuously acquired with temporal resolution of 2.1 seconds after intravenous injection of 0.1 mmol/kg of gadoteridol followed by a 20-ml saline flush at the rate of 2 ml/s. During DCE-MRI, patients were instructed to perform breath-hold in maximal end inspiration for as long as possible, and then repeat similar breath-holds as feasible for the duration of the acquisition. T1 maps were created before contrast injection using T1W images obtained with the same imaging sequence and parameters as above, but with different three flip angles (5°, 10°, 15°). For correcting motion in DCE-MR images, three post image-processing techniques were employed: unwarping, median filtering, and curve fitting. For unwarping, the boundary of a patient's body above the paravertebral muscle and abdominal aorta was determined in each DCE-MR image, then the boundary in each DCE-MR image was unwrapped to match with the boundary in the baseline image. All pixels within the boundary were relocated accordingly. Thereafter, median filtering and curve fitting were applied. T1 maps were also unwrapped as described above, and co-registered with DCE-MR images. A two-compartment pharmacokinetic model was employed to calculate volume transfer constant (K^{trans}) and reverse reflux rate constant (k_{ep}). In DWI analysis, the ADC value was calculated by finding the best fitting curve to the equation, $S = S_0 e^{-bD}$, where S is the intensity of DW images, S_0 is a constant, and D is ADC value.

Results: Figure 1A shows motion-corrected DCE-MR images (gray-scale) of a 48-year-old woman with a GIST at 30 seconds after initiating gadoteridol injection superimposed with K^{trans} and k_{ep} maps (color-scale) in the tumor regions, and DW images ($b=0$, gray-scale) superimposed with tumor ADC maps (color-scale). The same color-scale was applied for the three maps of each physiological parameter (K^{trans} , k_{ep} , or ADC) acquired before (baseline) and after therapy initiation. The initial GIST volume was 632 ± 178 cm³ (mean±SE), but decreased to 436 ± 182 cm³ and 272 ± 97 cm³ after weeks 2 and 6 of sunitinib therapy, respectively. The mean K^{trans} values were 0.026 ± 0.008 , 0.011 ± 0.004 , and 0.006 ± 0.001 min⁻¹ at 0 (baseline), 2, and 6 weeks after therapy initiation, respectively, while the mean k_{ep} values were 0.066 ± 0.015 , 0.032 ± 0.009 , and 0.027 ± 0.004 min⁻¹, respectively, during the same time periods. The initial mean ADC value was $1.03 \pm 0.16 \times 10^{-3}$ mm²/s, but increased to 1.76 ± 0.27 and $1.82 \pm 0.34 \times 10^{-3}$ mm²/s after weeks 2 and 6 of therapy, respectively. Figure 1B shows the changes (%) of GIST variables (volume, K^{trans} , k_{ep} , and ADC) following therapies, relative to the baseline values. Statistical significance was represented with either asterisks ($p \leq 0.05$) or hash marks ($p \leq 0.01$). Tumor K^{trans} change for 2 weeks was significantly correlated with tumor volume change during either 2 or 6 weeks ($p \leq 0.05$), whereas no correlation was detected between the changes of tumor volume, k_{ep} , or ADC value.

Discussion: Quantitative DCE-MRI and DWI were successfully utilized in GIST patients to measure the perfusion and diffusion parameters of tumors. Significant decreases of K^{trans} and k_{ep} values were observed in GISTs after sunitinib therapy, while tumor ADC values were significantly increased likely reflecting favorable anti-tumor effects. Tumor K^{trans} change was significantly correlated with tumor-volume change, and therefore it may serve as an effective surrogate biomarker, especially when applied at earlier time points, to assess the therapeutic efficacy of sunitinib, although data credibility would be strengthened with larger sample size.

