Tumor response assessment in patients with primary and advanced GIST no responsive to Imatinib Mesylate, undergoing second line molecular target therapy: early evaluation using Diffusion-Weighted Magnetic Resonance Imaging (DWMRI)

Poster No.: C-1383
Congress: ECR 2011
Type: Scientific Exhibit
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Keywords: Abdomen, Gastrointestinal tract, MR, MR-Diffusion/Perfusion, Chemotherapy, Neoplasia
DOI: 10.1594/ecr2011/C-1383

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Purpose

Background

Molecular diffusion is thermally induced random microscopic molecular motion, also known as Brownian motion. The properties of tissue diffusion are correlated with the presence of interstitial fluid and the degree of permeability. This molecular motion can be visualized with MR, since it provides a specific type of contrast. In general, neoplastic tissue tends to be characterized by lower diffusion coefficients than normal tissue due to the high cellular density and the abundance of intracellular and intercellular membranes.

In DWI image contrast is given by the intensity of the microscopic motion of water molecules. In order to make an MR sequence sensitive to diffusion, two gradients (diffusion gradients) on either side of a 180° radiofrequency pulse are added. The attenuation of the signal in DWI images depends on the diffusion factor b and the tissue apparent diffusion coefficient (ADC). The diffusion factor b represents the weighting factor of the diffusion sequences, and it determines the intensity and the duration of the diffusion gradients. The tissue ADC instead varies according to the tissue.

In GISTs, the normal structural architecture is replaced by spindle cells (around 70%) and to a lesser extent epithelioid cells (20%) or mixed (10%) and extensive stromal modifications such as perivascular hyalinization. These changes inhibit the motion of water molecules, thus producing a reduction in diffusion and ADC values in neoplastic tissue.

In the DWI sequences used in the study of GISTs multiple b-values are used (50, 400, 800, 1000 s/mm\(^2\)). In DWI, in a clinically relevant range of b-values (50-1000 s/mm\(^2\)), the following rules are applied: the higher the b-value, the higher the diffusion weighting and the greater the contrast in the pathologic region, which presents an elevated signal. Therefore it is advisable to calculate ADC maps from diffusion images obtained with at least two different b-values able to highlight pure diffusion coefficients pixel by pixel. Areas of reduced diffusion are given in the ADC maps by low signal.

Purpose

To evaluate the early tumor response to second line molecular target therapy in patients with primary and advanced GIST, no responsive to Imatinib Mesylate, using Diffusion-Weighted Magnetic Resonance Imaging (DWMRI).
Methods and Materials

17 pts with GIST (2 pts with primary duodenum GIST, 1 pts with primary gastric GIST, 6 pts with liver metastases, 2 pts with peritoneal involvement and 6 pts with hepatic and peritoneal metastasis) with 47 lesions were evaluated. All pts performed MR at baseline, and then at 2, 4, 6 months during treatment, using second line molecular target therapy (Sunitinib) and other drug (Nilotinib). All pts performed MR examinations with a 1.5T MR system using TSE T1w, TSE T2w, STIR, ce-3D-GRE T1w and DW sequences. DW MR acquisitions were performed using multiple b-values (50-400-800-1000 s/mm2). ADC maps were also calculated to obtain the main ADC values. DW MR images were qualitatively (signal of the lesion on high b values) and quantitatively (ADC maps) evaluated.
Results

7/17 patients (41%) were judged to be responsive to second line molecular target therapy after 6 months. Patients responsive to therapy showed: a) pre-treatment ADC values lower respect to non responding pts (Fig.1, Fig.2, Fig.3, Fig.4). b) reduction in signal intensity on high b values DW images after treatment (Fig.1, Fig.2, Fig.3). c) increase of ADC values after treatment (Fig.1, Fig.2, Fig.3). Responding lesions showed increase of ADC values since 2 months after treatment start.
**Fig. 0:** Liver metastasis of GIST with DWI technique before (a-d) and after molecular target therapy (e-h). The axial DWI images before treatment (a-c) show high signal of the lesion located in the II liver segment (arrows). After treatment the DWI images show a reduction in size of the lesion (response according to RECIST criteria) associated with a reduction in the signal hyperintensity of the images obtained with high b-value (g). The ADC maps shows an increase in the values going from 1.3x10^-3 before treatment (d) to 2.1x10^-3 (h) indicating a reduction in cellularity and therefore a response to treatment

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**Fig. 0:** Primary gastric GIST. Diffusion-weighted MR images: b50 (a), b400 (b), b800 (c) and ADC map (d) before treatment and after treatment b50 (e), b400 (f), b800 (g) and ADC map (h). The images obtained with low b-values (50-400) display elevated signal both in the active solid component (solid arrows) and the cystic-necrotic component (empty arrows). In the images obtained with elevated b-values (800) the solid component maintains its elevated signal (solid arrow), whereas the cystic-necrotic component...
shows a reduction in signal intensity (empty arrow). In the ADC map the active solid tissue appears hypointense (solid arrow), whereas the cystic-necrotic tissue is hyperintense (empty arrow). After treatment the DWI images show a reduction in the signal hyperintensity of the active solid component with high b-value (g). The ADC maps shows an increase in the values going from 1.1 x10-3 before treatment (d) to 1.2 x 10-3 (h) indicating a reduction in cellularity and therefore a response to treatment

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**Fig. 0:** Peritoneal metastases of GIST with DWI technique before (a-d) and after molecular target therapy (e-h). The axial DWI images before treatment (a-c) show high signal of the lesion located in the pelvis (arrows). After treatment the DWI images (e-g) show an increase in size (progression disease according to RECIST criteria) associated with a reduction in the signal hyperintensity of the images obtained with high b-value (i). The ADC maps shows an increase in the values going from 0.7 x10-3 before treatment (d) to 0.8 x10-3 (h) indicating a reduction in cellularity and therefore a response to treatment

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**Fig. 0:** Primary gastric GIST. DWI technique before (a-d) and after molecular target therapy (e-h). The axial DWI images before treatment (a-d) show high signal of the gastric lesion (arrow). After treatment the DWI images show an increase in size (progression disease according to RECIST criteria) associated with an increase in the signal hyperintensity of the images obtained with high b-value (g). The ADC maps show a decrease in the values going from $1.2 \times 10^{-3}$ before treatment (d) to $1.1 \times 10^{-3}$ (h) indicating an increase in cellularity and therefore a progression disease.

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Conclusion

Diffusion-Weighted Magnetic Resonance Imaging (DWMRI) can be useful in the prediction and early evaluation of tumor response to second line molecular target therapy in patients with primary or advanced GIST.

Although the limitations diffusion should be pointed out, which include the low spatial resolution and the lack of standardization of the acquisition protocols.
References


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