Measurement of T_1 values as a step towards absolute quantification of capecitabine and its metabolites in human liver by in vivo ^{19}F MRS at 3 Tesla

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Introduction

Predicting the sensitivity of a specific tumour to chemotherapy in cancer patients would enable individualisation of therapy, which could avoid unnecessary toxicity in non-responding patients. ^{19}F MR spectroscopy (^{19}F MRS) can be used to monitor the metabolism of fluorinated drugs. It has been suggested that an increased half-life of the chemotherapeutical drug 5-fluorouracil (5FU) as measured by ^{19}F MRS correlates with patient response to 5FU therapy (1). Knowledge of the tissue content of 5FU and its metabolites may provide further possibilities for the prediction of response to therapy. However, precise knowledge of the T_1 values of the drug and its metabolites is required to correct for saturation effects.

In patients with advanced colorectal cancer, oral capecitabine has shown comparable activity to intravenous (iv) 5FU (2,3). It is used as an alternative to iv 5FU treatment with increasing frequency, due to its ease of administration and favourable toxicity profile. Capecitabine is preferentially metabolized to 5FU in tumors and liver involving conversion into 5'deoxy-5-fluorocytidine (5'DFCR), followed by conversion into 5'deoxy-5-fluorouridine (5'DFUR). 5FU is further metabolized via different biochemical pathways to cytotoxic metabolites and 5FU catabolites like α-fluoro-β-alanine (FBAL) and 5-fluoro-ureido-propionic acid (FUPA). Recently we have shown that capecitabine and its metabolites can be measured by means of ^{19}F MRS (4). The aim of this study was to measureT_1 values of fluorine spins in capecitabine and its metabolites in human liver by *in vivo* ^{19}F MRS at 3 Tesla.

Patients and methods

MR measurements were performed on a 3 T Siemens Trio MR system. A flexible circularly polarized coil was used consisting of a 16cm circular coil and a 2 x 14cm butterfly coil. The coil is tunable to both 123MHz and 116MHz and connected to a home build interface with less than 0.1dB difference at both frequencies. Patients gave written informed consent and the study was approved by the local ethical committee.

To demonstrate the relevance of quantifying the tissue content of 5FU and its metabolites a CSI measurement (matrix 8x8x8, T_R=0.45s, FOV=300mm^3, hamming weighted acquisition with 12 averages) was performed to obtain localized ^{19}F MRS signals in the liver of one patient who was treated with oral capecitabine.

To get a proper estimate of the T_1 value of ^{19}F spins *in vivo*, progressive saturation measurements at three different repetition times were performed in 3 patients with colorectal cancer who were treated with oral capecitabine. Alternate measurement of 2 minutes (with the carrier frequency set between the resonance of capecitabine, 5'DFCR and 5'DFUR) or 1 minute (with the carrier frequency set to the FBAL resonance) each were performed using adiabatic half passage excitation with a repetition time (T_r) of 1000ms, 500ms or 250 ms. T_r's were changed interleaved in time. The total measurement time was 1 hour per patient. These T_1 values were used to correct for saturation using a reduced TR of 450ms for enhanced SNR per unit of time.

Results

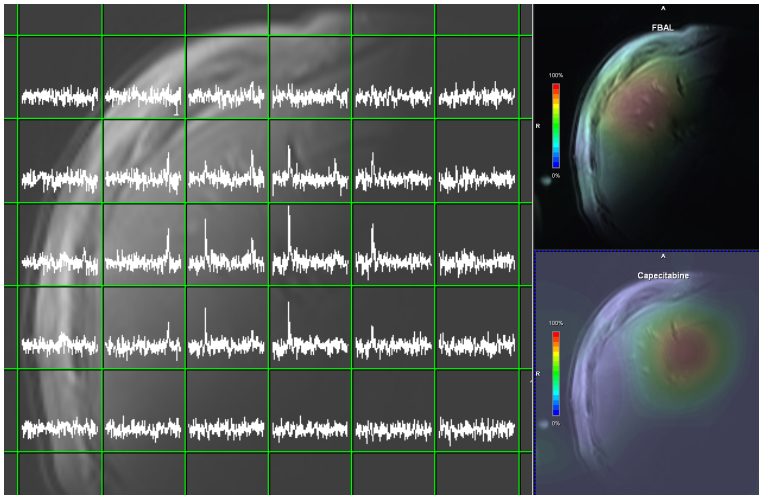

Fig. 1 CSI to measure ^{19}F MRS signals locally in the liver of a patient treated with oral capecitabine. Top right: color coded distribution of FBAL; bottom right: color coded distribution of capecitabine.

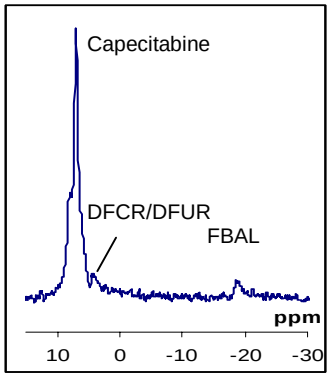

Fig. 2 ^{19}F MR spectrum of human liver showing capecitabine and FBAL (adiabatic excitation, T_R = 1000, 500 and 250ms, 30

	T_1 (s)
Capecitabine	0.2-0.3
DFCR/DFUR	0.3-0.5
FBAL	0.9-1.2

Table 1 T_1 values of fluorine spins in capecitabine, DFCR/DFUR and FBAL at 3T.

Fig. 1 shows the CSI of the ^{19}F MRS signals locally in the liver of one patient. Fig. 2 shows a typical spectrum from the progressive saturation measurements which are used for fitting of the T_1 values. In figure 3 the results of the progressive saturation measurements for capecitabine are shown and table 1 summarizes the calculated *in vivo* T_1 values for capecitabine and its metabolites.

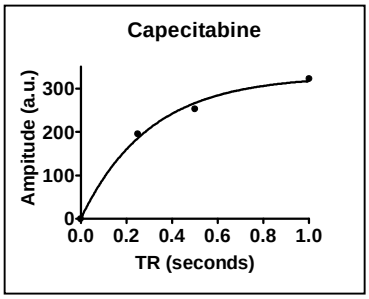

Fig. 3 Fitted amplitudes of ^{19}F MRS progressive saturation measurements for capecitabine

Discussion

In the CSI an inhomogeneous distribution of FBAL and capecitabine was observed in the liver, which underscores the relevance of quantifying the concentration of capecitabine and its metabolites. As can be seen from the from the color coded distribution of FBAL (fig. 1), the concentration of FBAL seems highest at the liver region close to the coil, which could be due to the coil B1 profile, rather than a physiological effect. Therefore, for quantification of the concentration of capecitabine and its metabolites a correction for the coil profile will also be necessary.

To our knowledge this is the first report of values of T_1 of capecitabine, 5'DFCR, 5'DFUR and FBAL at 3T. T_1 values for FBAL in human liver at 1.5T are reported, ranging from 0.12 s (5) to 1.6 s (6). Determination of the tissue content of capecitabine and its metabolites will be subject of further study.

References

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