Can Localised 19F MRS pharmacokinetics of 5FU in colorectal metastases predict clinical response?

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Introduction

5-fluorouracil (5FU) remains widely used in the treatment of colorectal cancer decades after its introduction. Using ^{19}F MRS in vivo, it is possible to monitor the pharmacokinetics of 5FU by measuring its half-life and metabolism to the inactive catabolite fluoro-β-alanine as well as the cytotoxic fluoronucleotides (FNuct) which are the basis of the anti-tumour activity. Previous clinical studies of a range of tumour types [1] using surface coils to study liver metastases have demonstrated improved patient survival associated with 5FU half-lives longer than 20 minutes, which Presant *et al* interpret as trapping of the drug within the tumour resulting in increased exposure of the cancer cells to FNuct.

Methods

We recruited 32 patients with histologically proven colorectal carcinoma prescribed a 5FU chemotherapy regime including bolus administration (400-425mg/m^2) . The primary focus was on patients with metastatic liver disease, but patients with no liver metastases who were receiving adjuvant 5FU therapy were also eligible. Subjects were scanned in a 1.5T GE Signa system using a 20x16cm surface coil tunable to either ^{1}H or ^{19}F. Gradient echo images were acquired to confirm the coil position, and T2-weighted fast spin echo images acquired from patients with liver metastases to better define the tumour volume. A fluorinated silicone oil reference at the coil centre was used for flip angle and frequency calibration. Spectra were acquired using a 90º pulse at the coil centre, TR=0.5s, 16kHz sweep width, 1k or 2k data points for 32 x 1-minute blocks, starting simultaneously with the 5FU administration. Data were analysed with the time-domain fitting program jMRUI. The half-life of 5FU was determined from the time-course data. Additionally, all time spectra for each subject were summed, fitted and assessed for the presence of the cytotoxic FNuct. After study completion, time to treatment failure (TTF) was obtained from routine clinical monitoring. Where T2-weighted data were available, the fraction of tissue signal emanating from tumour (fractional equivalent volume FEV) was calculated using a numerical model of the coil sensitivity.

Results

Of the 32 subjects, 15 had liver metastases and 17 did not. FNuct signals were detected in 5 of the subjects with liver metastases and in 7 metastasis-free subjects. Unexpectedly, comparison of survival curves for the patients with metastases showed that high levels of FNuct were associated with poorer survival (Mantel-Cox test, p=0.027) (Figure 1); this is surprising as, intuitively, higher levels of FNuct should result in better cell killing and improved survival. The observed 5FU half-life values ranged from 4.0-15.5 mins, mean+/-SEM 8.0+/-0.48. Since they were all<20mins, none fell into the "trapper" category of Presant *et al*. Presence or absence of liver metastases made no significant difference in 5FU half-life (t-test, p=0.2). There was no significant relationship between 5FU half-life and TTF, either in the whole population or in the group with hepatic metastases. Paired survival curves showed an expected highly significant increase in TTF in the metastasis-free group. FEV values were available from 10 subjects with liver metastases and T2w MRI of interpretable quality. There were two very high FEV values of 0.49 and 0.52, the remainder ranging from 0.05-0.27. There was no significant association between FEV and TTF or 5FU half-life, though the patients with the two highest values had long half-lives of 15.5 and 9.4 minutes.

Conclusions

With the large coil used in this study, it is possible to detect FNuct in liver and tumour tissue. The similarity in 5FU half-life of patients with and without liver metastases suggests that the observed signal may be dominated by normal liver metabolism except when the metastatic load is very high; notably, the two subjects with the highest FEV values had long 5FU half-lives. There is no clear association between 5FU half-life and outcome, though the half-lives observed in this study are shorter than those associated with improved outcome in the literature. High FNuct levels appear to be associated with poorer outcome as measured by TTF; this is likely to reflect higher metastatic load since FNuct is more likely to be produced in tumour cells. Future studies of liver metastases may benefit from operating at higher field strengths and using chemical shift imaging to isolate tumour metabolism.

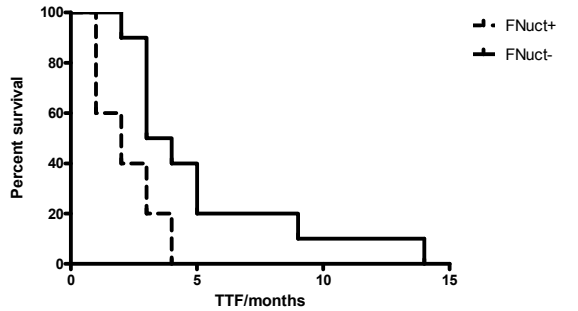

Figure 1. Survival curves demonstrating poorer survival of patients with liver metastases with detectable fluoronucleotides in 19F liver spectra

1. Presant, C.A., et al., *Association of intratumoral pharmacokinetics of fluorouracil with clinical response.* The Lancet, 1994. **343**(8907): p. 1184-1187.