In vivo 19F magnetic resonance spectroscopy of low dose fluorinated methotrexate in solid tumors

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PURPOSE

(1) to demonstrate the possibility of in vivo detection and measurement by ^{19}F-MRS of a low and intermediate dose (100-250 mg/kg) administration of a fluorinated version of the chemotherapeutic antifolate agent methotrexate (F-MTX)
(2) to show he possibility of in vivo ^{19}F-MRS to discriminate between the real time tumor tissue concentration of different F-MTX metabolites with different chemical shifts and with known different cytotoxic potencies

INTRODUCTION

Previous reports have shown the in vivo use of ^{19}F-MRS to assess tumor resistance to high dose (400mg/kg) antifolate therapy in mice [1]. A resistance assay method was developed showing a linear correlation between the tumor tissue concentration of F-MTX and the therapeutic response [2]. Besides the risk of serious complications induced by high dose chemotherapy, there is an increased interest in low dose chemotherapy because of its anti-angiogenic effect on tumor tissue [3]. Equally important to introduce ^{19}F-MRS as a valuable tool in the clinic, is the ability to discriminate the ^{19}F signal of the active compound from the signal of metabolites of F-MTX, the latter which have shown to exhibit reduced or no cytotoxic effect at all.

EXPERIMENTAL METHODS

Experiments were performed on a small animal 7 Tesla Bruker Biospin spectrometer (30 cm horizontal bore). An in-house built three turn solenoid coil was used (diameter = 10 mm). Animals were scanned in a temperature controlled water bath to allow for susceptibility matching [3]. A non-resistant human sarcoma cell line HT-1080 and a resistant human sarcoma cell line MD-805 were used as tumor xenografts, by injecting 0.2 ml of ~10^6 cells subcutaneously into the flanks of 6-week old female nude mice. The animals were scanned when the tumor reached a size between 0.3 and 0.4 cm^3. F-MTX was administered via intravenous (i.v.) bolus tail-vein injection at a dosage of 100mg/kg and 250 mg/kg, corresponding to a low and intermediate dosage in clinical use. Acquisition parameters for the ^{19}F-MRS experiments included a 45° pulse angle and a pulse repetition of 0.7 s with 3000 transients/spectrum (35 min/spectra). To quantify tumor tissue concentration of F-MTX we used an external reference standard of 0.02 M of trifluoro-acetic acid (TFA) in D_20. Appropriate correction factors were used for the effects on the resonance line intensity of incomplete saturation and slightly different tumor size.

RESULTS

Figure 1 shows the F-MTX tumor concentration obtained via ^{19}F MRS with a 35 minute temporal resolution, following 100mg/kg i.v. bolus dosage. The in vivo pharmacokinetics of the tumor tissue shows a variation in drug uptake/retention and absolute concentration between the HT-1080 and MD-805 tumors. The MTX sensitive HT-1080 achieves a peak concentration at ~100 minutes (n ~ 0.46 mM) post injection whereas the non-sensitive MD-805 clearly shows a reduced uptake and a significantly lower absolute concentration, with no evident maximum peak. Figure 2 shows the stacked ^{19}F spectra with 35 minutes temporal resolution following an intermediate dosage of F-MTX of 250mg/kg. Two ^{19}F peaks shifted by ~0.33ppm are observed with different pharmacokinetics. Figure 3 shows a plot of the relative intensity of the two peaks, respectively proportional to the tumor tissue concentration of F-MTX (peak A) and its metabolite (peak B). Peak A is retained for longer times and achieves a maximum at around 260 minutes while peak B rises and falls in a much shorter time frame (100-270 minutes). Low dose administration (100mg/kg) showed a single peak spectra, with no discrimination between MTX and its metabolite.

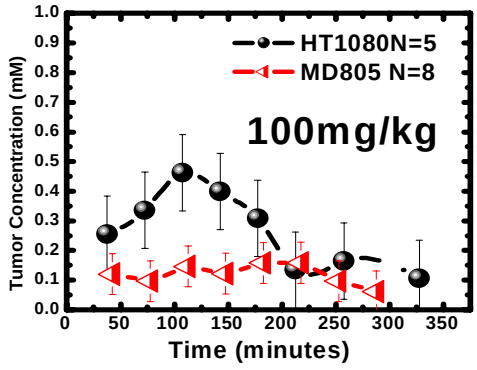

Figure 1

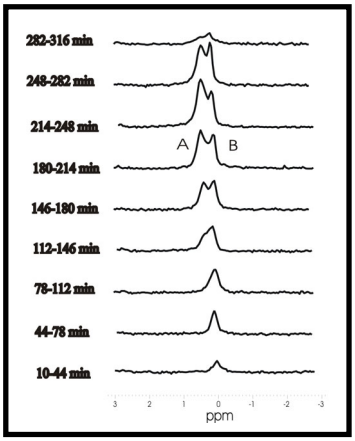

Figure 2

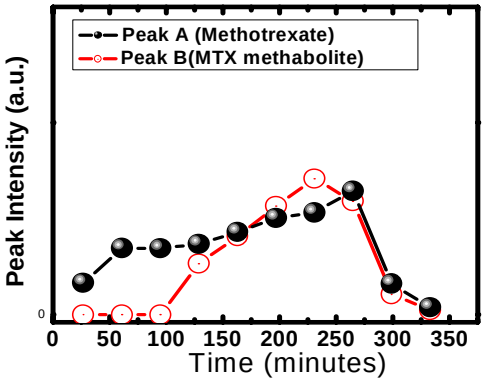

Figure 3

CONCLUSION

^{19}F-MRS is a sensitive tool for in vivo monitoring of low dose chemotherapy of F-MTX and allows to differentiate F-MTX from its less active metabolite following intermediate dose. The different time course between the data at low and intermediate dose appears to be dose dependent. ^{19}F-MRS is a promising clinical tool for in vivo monitoring of F-MTX and has the potential to predict early treatment response.

REFERENCES

[1] W. Spees et al., *Mol Cancer Ther*., 2(10), pp 933-9, 2003 [2] W. Spees et al. *Clin. Cancer Res*. (in press), [3] B. Lennernas et al., *Acta Oncologic*a, 42 (4), pp 294-303, 2003