DMSO as a potential contrast agent for brain tumours

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INTRODUCTION: Dimethyl Sulfoxide (DMSO) has been reported to act as an anti-inflammatory and an anti-oxidant compound, commonly used in clinical trials to treat interstitial cystitis [1]. It has also been used as administration vehicle for some drugs, such as temozolomide (TMZ) [2]. Moreover, exogenous dimethyl sulfone (MSM) resonance has also been described in human brain by MRS [3].

PURPOSE: After detecting a DMSO resonance in mouse brain during TMZ treatment, our goal was to characterize its entry/wash-out kinetics in normal brain parenchyma and in GL261 tumours, and its potential as a possible contrast agent for brain tumours.

MATERIALS AND METHODS: Nine C57BL/6 female mice were used in this study, 3 wild-type (WT) mice and six glioma-bearing mice induced as described in [4]. MRI studies were carried out at 7T in a horizontal magnet, anesthetizing the animals with isoflurane (1.5-2.0 %), monitoring their breathing pattern and controlling their rectal temperature (37ºC).
Initially, TMZ was diluted in DMSO and administered by an intragastric probe to three WT mice used as controls. The administration vehicle was DMSO in saline (10%). Standard T2-weighted MRI scout images (TR/TEeff= 4200/36ms) and PRESS single-voxel (SV) (2.5mm)^3 spectra (TE=12 and 136ms) were acquired from the striatum before and after a single dose administration of TMZ solution. This protocol was performed at different times after treatment to calculate the DMSO wash-out curve in normal brain. Afterwards, the same protocol was applied to three GL261 glioma-bearing mice to further investigate the acute effects of the DMSO in their brain tumour spectral pattern. Only the administration vehicle was used in this case. SV-MRS post-processing was performed with MestRec software (Mestrelab Research SL). The areas of selected metabolites were normalized to unsuppressed water and used for quantification.
The other 3 tumour-aflicted mice were studied by MRSI before and after vehicle administration, which was injected intraperitoneally (i.p.) to avoid re-shimming needs. A reference T_{2W} image and 12 ms TE control MRSI were initially acquired. DMSO was then injected (0min_PI_DMSO), followed by 14 repeated 12ms TE MRSI acquisitions, interleaved with two 136ms TE MRSI at 110min_PI_DMSO and 242min_PI_DMSO. Parameters for PRESS-MRSI: 1.76x1.76x1.0cm FOV; 5.5x5.5x1.0mm VOI; 512 scans; 32x32 reconstructed matrix (4.84µl nominal resolution); 2500ms TR (21m30s acquisition time), 12 ms TE; signal sampled with 2k points. MRSI grids were post-processed with 3DiCSI [5] and exported in ASCII format to MatLab (home-written scripts) to generate time-course maps of brain MR-detectable DMSO changes based on peak heights.
Statistical analysis used was ANOVA, setting significance at p<0.05.

RESULTS: The DMSO signal (2.72ppm) was detected by SV MRS in WT parenchyma and in GL261 tumours 30min after its administration, and it remained visible for 5-6 hours. The wash-out kinetics of DMSO was significantly different between both regions (tumour and normal brain), remaining detectable for a longer time and reaching higher concentrations in the tumour (Figure 1). These differences were also observed in MRSI studies, where a clear "hot-spot" of DMSO was visible inside the tumour (Figure 2), reaching its maximum intensity between 22 and 88 min after i.p. injection.

CONCLUSIONS: DMSO produces a clear contrast between GL261 mouse glioblastoma and nearby/peritumoral brain parenchyma. In addition, this compound crosses the blood-brain-barrier (BBB), as its signal is also visible in WT mice brain parenchyma. This suggests that it may also produce visible enhancement in low-grade brain tumours with an intact BBB. Further experiments are in course for a better understanding of the DMSO kinetics in the tumour and to improve its application for tumour detection and monitoring.

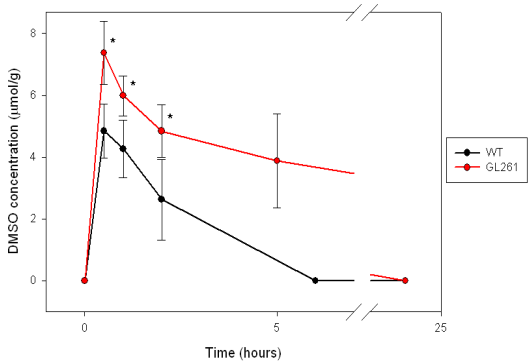

Figure 1: DMSO wash-out curves from normal brain tissue of WT mice and from GL261 tumours after intragastric administration. DMSO concentrations were calculated from 12ms SV spectra using the water signal as an internal standard. The maximum concentration was reached 30min after administration and the DMSO signal remained visible for 6 hours. * These values were statistically different between both curves (p<0.05).

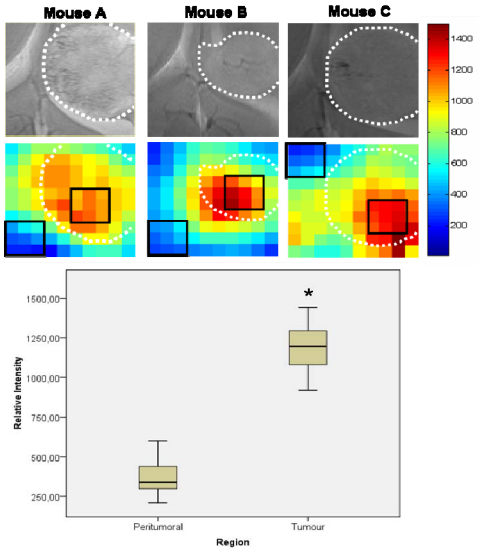

Figure 2: *In vivo* monitoring of DMSO in 3 GL261 tumours. Row 1, voxel location in T_{2W} reference image (5.5x5.5mm) for MRSI sequences acquired in three tumour-bearing mice (A, B and C). Row 2, DMSO maps of the maximum signal intensity detected after injection in each animal (at 88min in A, 44min in B and 22min in C). In all cases the DMSO concentration was higher inside the tumour (white dotted contour) than in peritumoral regions, as it is shown in the box-plot graph below. Relative DMSO intensities were calculated from the tumoral and peritumoral regions marked with black squares inside the maps, and their average values were represented *(p<0.01).

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