Improving the Diagnostic Efficacy in Pathological Models with Novel High Relaxivity Gadolinium Chelates

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Gadolinium based contrast agents (GBCAs) have been widely used in clinic to enhance the quality of images acquired during Magnetic Resonance Imaging (MRI) acquisitions. Currently, GBCAs are used in 40% of MRI scans and 60% of neuro MRI scans, corresponding to approximately 40 million worldwide administrations per year (1). GBCAs associated fatalities are really rare (40 serious events and 0.9 deaths per million). Nevertheless, during the last five years their safety has been under discussion after the reported experimental evidence of MR signal hyper-intensity in certain brain regions in unenhanced images (2) due to the presence of gadolinium retention following repeated administrations of GBCAs (3). In this scenario, where the GBCAs are largely used in clinic, but at the same time new concerns are emerging, the research of new Gd-chelates with high relaxivity (to improve the detection of small lesions and/or reduce the administered dose) and improved kinetic inertness and chemical stability (to decrease the amount of gadolinium retained) is undergoing to a new boost. This PhD thesis is inserted in this challenging context, and specifically is aimed to test two novel high relaxivity GBCAs on healthy animals and on different pathological models as a first step for translation to clinical trials. All the pathological models were selected to guarantee a suitable preclinical development and the induction procedure was optimized to obtain a feasible and reproducible protocol, associated to a reduced pain and stress of the animal, in accordance to the 3Rs guidelines. In the first part of the thesis, a linear, dimeric, albumin binder GBCA was fully characterized in vitro in terms of relaxometric properties and then its bio-distribution was evaluated on healthy animals and on a pathological model of ischemia. $(Gd\text{-}DTPA)_2Chol$, presented a series of features, such as good affinity for albumin, high number of binding sites, properties of carrying two Gd ions per molecule, and limited hepatobiliary elimination. These properties contributed to an unexpected long blood elimination half-life, resulting into an optimal confinement in the vascular space and thus into an extension of the available time window for MR angiography. In the second part, a dimeric macrocyclic GBCA, selected as possible candidate for clinical translation, was tested for its pharmacokinetics and its efficacy on a series of pathological models: glioma, meningioma, cerebral ischemia and breast cancer (Fig.1). The compound, namely Lead, presented good relaxometric properties and stability in vitro, and preclinical studies demonstrated that had the same efficacy of commercial compounds, i.e. Gadovist® and Dotarem®, when injected at the half dose 0.05 mmol Gd/kg and an efficacy approx. two times higher when injected at the same dose, i.e. 0.1 mmol Gd/kg.

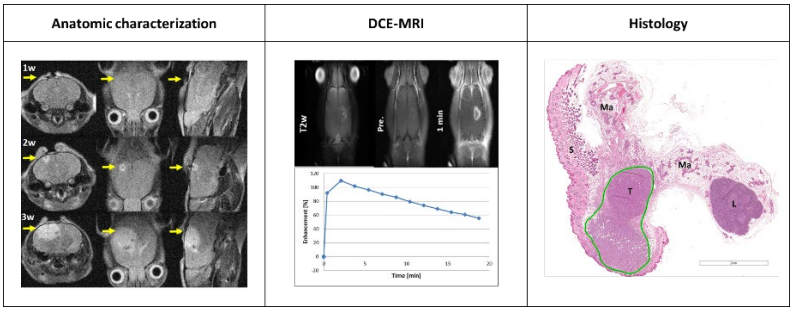

Figura 1 a) MRI anatomic characterization of Convexity Meningioma; B) DCE MRI of a cerebral ischemia ; C) Transversal histological section of a mammary breast tumor.

1) Runge, et al. Invest. Radiol. 2017, 52, 317–323
2) Kanda et al. Contrast Material. Radiology (2014) 270: 3
3) Mc Donald et al. Radiology (2015) 275:772–782