Magnetic Resonance Imaging 46 (2018) 98–105

Contents lists available at ScienceDirect

Magnetic Resonance Imaging

journal homepage: www.elsevier.com/locate/mri

Original contribution

Evaluation of dynamic contrast-enhanced MRI biomarkers for stratified cancer medicine: How do permeability and perfusion vary between human tumours?

Ross A. Little[a], Hervé Barjat[b], Jennifer I. Hare[c], Mary Jenner[b], Yvonne Watson[a], Susan Cheung[a], Katherine Holliday[a], Weijuan Zhang[a], James P.B. O'Connor[d], Simon T. Barry[c], Sanyogitta Puri[e], Geoffrey J.M. Parker[a,f], John C. Waterton[a,b,f,*]

[a] Centre for Imaging Sciences, Division of Informatics Imaging & Data Sciences, School of Health Sciences, Faculty of Biology Medicine & Health, University of Manchester, Manchester Academic Health Sciences Centre, Manchester M13 9PL, UK
[b] Formerly AstraZeneca, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK
[c] IMED Oncology, AstraZeneca, Li Ka Shing Centre, Cambridge CB2 0RE, UK
[d] Division of Cancer Sciences, Faculty of Biology Medicine & Health, University of Manchester, Manchester Academic Health Sciences Centre, Oxford Road, Manchester M13 9PL, UK
[e] AstraZeneca, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK
[f] Bioxydyn Ltd., Rutherford House, Manchester M15 6SZ, UK

ARTICLE INFO

Keywords:
Drug delivery
Dynamic contrast-enhanced MRI
Enhanced permeability and retention
Imaging biomarkers
Personalised medicine
Solid tumours

ABSTRACT

Background: Solid tumours exhibit enhanced vessel permeability and fenestrated endothelium to varying degree, but it is unknown how this varies in patients between and within tumour types. Dynamic contrast-enhanced (DCE) MRI provides a measure of perfusion and permeability, the transfer constant K^{trans}, which could be employed for such comparisons in patients.

Aim: To test the hypothesis that different tumour types exhibit systematically different K^{trans}.

Materials and methods: DCE-MRI data were retrieved from 342 solid tumours in 230 patients. These data were from 18 previous studies, each of which had had a different analysis protocol. All data were reanalysed using a standardised workflow using an extended Tofts model. A model of the posterior density of median K^{trans} was built assuming a log-normal distribution and fitting a simple Bayesian hierarchical model.

Results: 12 histological tumour types were included. In glioma, median K^{trans} was 0.016 min^{-1} and for non-glioma tumours, median K^{trans} ranged from 0.10 (cervical) to 0.21 min^{-1} (prostate metastatic to bone). The geometric mean (95% CI) across all the non-glioma tumours was 0.15 (0.05, 0.45) min^{-1}. There was insufficient separation between the posterior densities to be able to predict the K^{trans} value of a tumour given the tumour type, except that the median K^{trans} for gliomas was below 0.05 min^{-1} with 80% probability, and median K^{trans} measurements for the remaining tumour types were between 0.05 and 0.4 min^{-1} with 80% probability.

Conclusion: With the exception of glioma, our hypothesis that different tumour types exhibit different K^{trans} was not supported. Studies in which tumour permeability is believed to affect outcome should not simply seek tumour types thought to exhibit high permeability. Instead, K^{trans} is an idiopathic parameter, and, where permeability is important, K^{trans} should be measured in each tumour to personalise that treatment.

1. Introduction

Personalised medicine creates an enhanced role for imaging biomarkers [1]. In oncology, for example, some patients fail to benefit from medical treatment simply because the drug fails to reach its site of action. Imaging biomarkers may identify patients whose tumours are accessible to drug treatment. Such imaging biomarkers would be of broad interest. Drug developers may prefer trials of such drugs to be

* Corresponding author at: University of Manchester, Stopford Building, Oxford Road, Manchester M13 9PL, UK.
E-mail addresses: ross.little@manchester.ac.uk (R.A. Little), herve.barjat@stfc.ac.uk (H. Barjat), Jennifer.Hare@astrazeneca.com (J.I. Hare), Yvonne.Watson-2@manchester.ac.uk (Y. Watson), Susan.Cheung@manchester.ac.uk (S. Cheung), kholliday@mcrc.man.ac.uk (K. Holliday), weijuan.zhang@merck.com (W. Zhang), James.O'Connor@manchester.ac.uk (J.P.B. O'Connor), Simon.T.Barry@astrazeneca.com (S.T. Barry), Sanyogitta.Puri@astrazeneca.com (S. Puri), geoff.parker@manchester.ac.uk (G.J.M. Parker), john.waterton@manchester.ac.uk (J.C. Waterton).

https://doi.org/10.1016/j.mri.2017.11.008
Received 12 July 2017; Received in revised form 8 November 2017; Accepted 13 November 2017

stratified by tumour permeability so as to identify the groups most likely to benefit. Regulatory authorities may demand a predictive biomarker to contraindicate drug in patients with low tumour permeability who are least likely to benefit. Oncologists want to personalise treatment by selecting drugs most likely to reach their target and benefit patients: radiologists want to identify those patients.

A systemic drug normally arrives in the tumour via the vasculature, but to reach its target on a neoplastic cell, it must first traverse the vascular endothelium. Enhanced perfusion and vascular permeability in tumours are expected to accelerate the arrival of a drug at its target and may enhance retention of macromolecules [2,3]. This enhanced permeability and retention effect is viewed as a universal property of solid tumours [4], but the lack of comparative data assessing tumour perfusion and permeability in human subjects has hindered the evaluation of its clinical relevance for different classes of therapies [5]. The effect is likely to be more variable and complex in humans than in mouse models [6,7]: one imaging study showed therapeutic liposome accumulation to vary between 5% and 30% of the injected dose per weight of tumour [8]. Such heterogeneity has clinical implications: patients and tumours with high levels of drug accumulation may receive therapeutic benefit, while patients with low accumulation will only experience off-target adverse effects.

Dynamic contrast-enhanced (DCE)-MRI and DCE-CT rely on enhanced tumour uptake of contrast agents, reflecting enhanced perfusion and permeability. However, while radiologists commonly observe that particular tumours are 'highly enhancing', they do not routinely quantify their visual impression in a way that allows precise between-patient and between-centre comparisons. DCE-MRI and -CT also allow calculation of the transfer constant K^{trans}, which quantifies the permeability-surface area [9]. K^{trans} and related metrics have been successfully employed as pharmacodynamic biomarkers in over 100 clinical studies of anti-vascular agents as well as numerous studies of tumour biology [10] in different studies and centres [10,11]. However, few studies included > 40 patients [12], and the DCE-MRI biomarkers were not generally measured in a consistent or standard way. While change in K^{trans} can be compared between studies [13], baseline values cannot. This lack of standardisation poses a significant impediment [14], preventing objective comparison of permeability-driven enhancement of different tumour types. There is therefore a need for larger analyses to evaluate the pre-treatment parameters for stratifying tumour permeability.

In planning the development of an investigational new cancer medicine, it is important to select the tumour types most likely to respond. Our hypothesis was that tumour types exhibit systematic differences in permeability and perfusion, and consequently in K^{trans}. The null hypothesis was therefore that K^{trans} is an idiopathic parameter that must be individually measured in each patient and each tumour. To test our hypothesis, a standardised analysis of tumour K^{trans} was performed in 12 tumour types in 230 patients from baseline DCE-MRI datasets accumulated from previously completed clinical imaging trials, to enable direct comparison of individual tumours and tumour types. The resulting reference data set was analysed for inter-disease, intra-patient, and intra-tumour heterogeneity in vascular endothelial permeability-driven contrast agent accumulation. This DCE-MRI-based analysis aimed to provide insight into the variation in perfusion and permeability across a broad patient and tumour population.

2. Materials and methods

2.1. Data sets

We accessed a databank of quantitative DCE-MRI studies conducted in our centre over 15 years, largely for the evaluation of putative therapeutic treatments. A single baseline scan from each eligible patient (Fig. 1) in this databank acquired up to May 2013 was analysed in this study using the same software and workflow throughout. Ethical approval was given by the Proportionate Review Sub-Committee of the NRES Committee South Central Berkshire for reanalysis of the data, and informed consent had been provided by the patients. Patients had undergone DCE-MRI with measurements made before, during and after bolus injection of a standard dose (0.1 mmol/kg) of either gadodiamide (Omniscan, GEHC) or gadoterate (Dotarem, Guerbet) via the antecubital vein using a Medrad Spectris power injector (Bayer AG) at a rate of 3 ml/s followed by an equal volume saline flush, also at 3 ml/s. Inclusion criteria for this study were: a consistent data acquisition protocol (a 3D fast field echo protocol with baseline T_1 quantification data acquired using a range of flip angles, and a dynamic acquisition using a constant flip angle); acceptable data acquisition quality; and approval by the original study sponsor. Similar scanning protocols were chosen to allow meaningful direct comparison of the resulting biomarkers, see [15–22] and Table 1.

2.2. Patient characteristics

A total of 230 patients had tumour data suitable for analysis. 45% were male. Median weight was 73 kg (range 44–120). Median age was 62 (range 26–81). The patient cohort contained 342 imaged tumours (with a range of 1 to 7 tumours per patient). Table 2 shows the number of tumours classified by type, as well as the number of patients with that tumour type. A breakdown of patient ages, weights and tumour volumes is shown in Supplementary material.

Just over half (54%) of the imaged tumours were from patients with colorectal primaries. A further 21% were from patients with ovarian primaries. Patients with gliomas and prostate primaries formed the next largest groups of 10% and 5% of tumours respectively.

2.3. DCE-MRI analysis

The data were analysed using in-house analysis software. To ensure comparability of data across studies, all the datasets were analysed from the source signal intensity magnitude files following a prespecified set of standard procedures. All datasets were reviewed to verify that the source data had been acquired in compliance with the original study protocol, and the data were not motion-corrupted. Delineation of the tumour volume region-of-interest (ROI) was normally performed on anatomical, not DCE, images. All ROIs were drawn by a radiographer trained and experienced in tumour definition in MRI (YW; 15 years' experience). Blinding was obviously impossible, because the anatomic location of the tumour is evident in the image. Where an ROI was already available in the dataset, this was reviewed before inclusion into this study. Where no ROI was present or usable, new ROIs were drawn. The ROI was then formed into a mask volume, which was used for the analysis. Both the ROI and the mask were reviewed during a quality control step, in which a second individual checked the lesion edge was properly defined and no obvious errors (such as missing slices) were present. The mask was also checked to ensure that propagation onto the dynamic data set had worked as expected (i.e. the mask lay over the target lesion and was not corrupted). Whole tumour volume measurements (mm^3) were made for each tumour by summing the volume of the voxels in the region of interest.

Baseline T_1 maps for each patient were calculated voxelwise by Levenberg-Marquardt minimisation across three volumetric acquisitions using a set of flip angles shown in Table 1 and applying the fast field echo equation (Eq. (1)) to solve for T_1 and M_0 [24]. Dynamic MRI signal was converted to voxel-wise contrast agent concentration as a function of time [24–26] assuming a linear relationship between concentration and change in relaxation rate (Eq. (2)), where r_1 is the respective longitudinal relaxivity: 3.6 $s^{-1}{\cdot}mM^{-1}$ for gadoterate at 1.5 T; 4.3 $s^{-1}{\cdot}mM^{-1}$ for gadodiamide at 1.5 T; or 4.0 $s^{-1}{\cdot}mM^{-1}$ for gadodiamide at 3 T [27].