Population analysis of the DCE-MRI response of liver metastases to a single dose of bevacizumab in CRC patients

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OBJECTIVES: Our objective is to analyze the time course of the K^{trans} response to a single dose of bevacizumab (bev) based on Dynamic Contrast Enhanced MRI data from a previously published phase II clinical trial [1], where K^{trans} is a measure of vascular permeability to contrast agent, surface area and rate of tissue perfusion. Decrease in K^{trans} is observed shortly after dosing, however, the subsequent dynamics of this parameter over a 12 day period are not entirely clear due to inter-patient variability.

METHODS: 2 baseline (3 and 2 days predose) plus 4 subsequent DCE-MRI scans following a single 10 mg/kg dose of bev (4hr, 2d, 8d and 12d) were obtained from 10 patients, each with between 1-6 colorectal liver metastases (26 lesions total). Two patients had missing data points; the first (4 lesions) missed the 8d scan while the other (3 lesions) missed the 8d and 12d scans. K^{trans} values for each scan were estimated [1] using the extended Tofts version of the Kety compartmental model [2]. K^{trans} dynamics plus inter-individual (IIV) and inter-lesion (ILV) variability were described using an indirect response model with feedback, implemented in NONMEM. True individual baseline K^{trans} was estimated for each lesion by assuming that it varies around the observed average baseline with variance $\sigma^2/2$ [3]. Post-hoc analysis provided parameter estimates for each lesion and simulated K^{trans} profiles were produced using the estimated population mean and variance parameters.

RESULTS: ILV was not identifiable and was assumed to be zero, except for inter-lesion variability in baseline K^{trans}. Inter-patient variability was significant. IIV of model parameters is identifiable and estimated to be larger for parameters in the indirect response equation than for the feedback equation (66% CV vs. 48% CV). The predicted population response describes a rapid decrease of K^{trans} to 57% of baseline followed by a slower return to baseline within 12 days after a single dose of bev, with rebound over baseline in some patients.

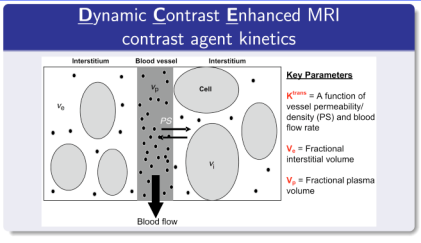
CONCLUSION: There is a significant amount of inter-patient variability (IIV) in K^{trans} response to a single dose of bev; inter-lesion variability (ILV) is not detectable within these data. However, a population trend of fast decrease of K^{trans} to 57% of baseline followed by a return to baseline within 12 days is clear from this analysis. Based on data from a previous PK analysis, this does not appear to be driven by a decline in plasma bevacizumab concentration.

REFERENCES

[1] O'Connor et al. Quantifying antivascular effects of monoclonal antibodies to vascular endothelial growth factor: insights from imaging. Clin Cancer Res. 2009 Nov 1;15(21):6674-82

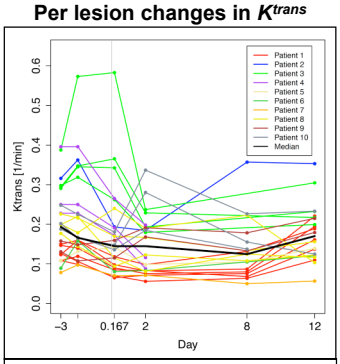
[2] Tofts PS, Kermode AG. Measurement of the blood-brain barrier permeability and leakage space using dynamic MR imaging. 1. Fundamental concepts. Magn Reson Med. 1991 Feb;17(2):357-67.

[3] Port RE et al. Predicting the time course of haemoglobin in children treated with erythropoietin for renal anaemia. Br J Clin Pharmacol. 1998 Nov;46(5):461-6.



A contrast agent (black circles) is injected into the patient just prior to start of data aquisition; changes in blood and tissue concentration are measured by the MRI scanner [Figure (modified) from: O'Connor et al. Br J Cancer. 2007 Jan 29;96(2):189-95]

Per lesion changes in K^{trans}



Inter-patient/inter-lesion variability. Data from 1 to 6 lesions from 10 patients is shown; 2 baseline scans (0 and 1 days) plus 4 post-dose scans (3.167, 5, 11, 15 days) indicated by circles. Single 10 mg/kg dose of bevacizumab administered at day 3 (vertical line). Black line indicates median values across all patients and lesions at each time point.

Model structure

The model equations are written as

$$\frac{d[K^{trans}(t)]}{dt} = k_{in}R(t) - k_{out}K^{trans}(t) \quad (1)$$

and

$$\frac{d[G(t)]}{dt} = \left[1 - \frac{K^{trans}(t)}{K^{trans}(0)}\right] k_{tol}, \quad (2)$$

and

$$L(t) = \begin{cases} 1 & t < 3 \\ 0 & t \geq 3 \end{cases} \quad (3)$$

where $R(t)$, the pharmacodynamic response function, describes the response of k_{in} to bevacizumab and is written as

$$R(t) = L(t) + G(t). \quad (4)$$

Initial conditions for the state variables are

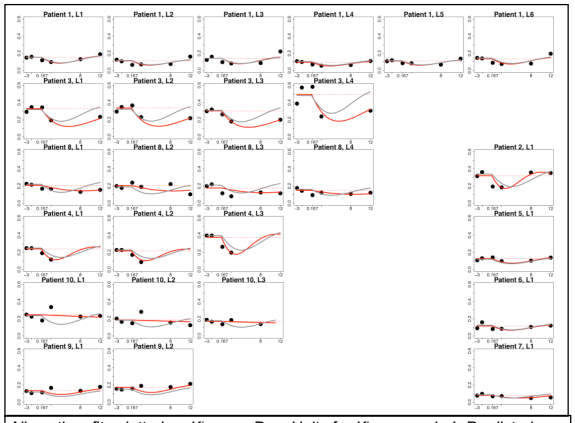
$$K^{trans}(0) = \frac{k_{in}}{k_{out}} \quad (5)$$

and

$$G(0) = 0. \quad (6)$$

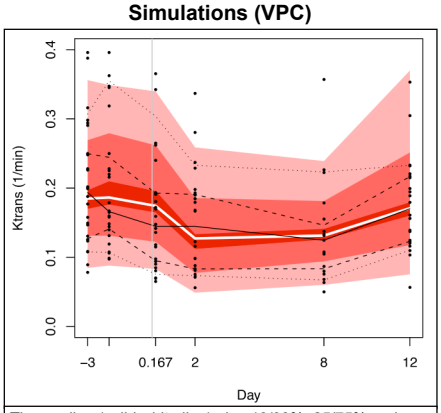
Model consists of 2 ODEs and the rectangle function, L(t). Three parameters are fitted to patient data: 1) k_{out}, 2) k_{tol} and the baseline K^{trans} value, 3) $K^{trans}(0)$.

Population and per patient post-hoc fits



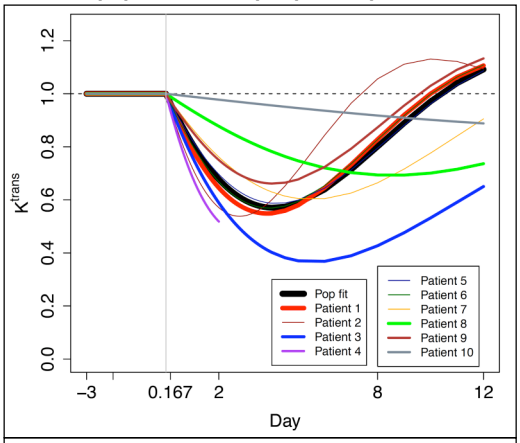
All posthoc fits plotted as K^{trans} vs. Day. Units for K^{trans} are min^{-1}. Predicted response based on estimated population values is shown in grey for each plot. Estimated residual SD = 0.03567.

Simulations (VPC)

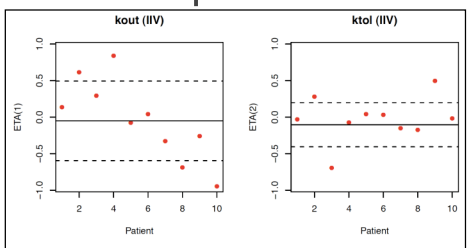


The median (solid white line) plus 10/90%, 25/75% and 45/55% quantiles of simulations are shown (shaded regions) along with observed K^{trans} values for each DCE-MRI scan (circles) [10/90%, 25/75% quantiles and medians of the observed values are indicated by dotted, dashed and solid black lines]. Bev administered at day 3 (vertical line).

Scaled population and per patient post-hoc fits



Predicted population response (black) shown with all individual posthoc fits. Each fitted curve is scaled to its baseline value. Line thickness is proportional to number of lesions. Bevacizumab administered at day 3 (vertical line).



	k_{out}	k_{tol}
Population Mean	0.212	0.483
%CV	65.7	47.6

Inter-individual variability (IIV) for ETA values associated with k_{out} and k_{tol}. Solid and dashed lines represent mean and SD.

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