A population model for clinical DCE-MRI response to a single dose of bevacizumab

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Objectives

Our objective is to develop a mathematical model that describes the time course of K^{trans} response to a single dose of bevacizumab (bev) based on Dynamic Contrast Enhanced MRI data from a previously published post-licensing study [1], where K^{trans} is a composite measure of vascular permeability to contrast agent, surface area and rate of tissue perfusion. It is known that a rapid decrease in K^{trans} occurs 4 hours after dosing, however, the subsequent dynamics of this parameter over a 12 day period are not entirely clear due to strong inter-patient variability.

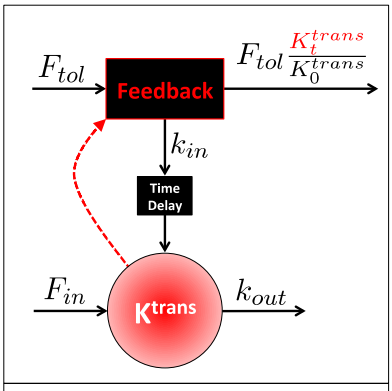

Figure 1. Model Structure. F_i represents rate of flux (K^{trans}/day) and k_i represents fractional transfer (1/day). $K^{trans}(0)$ is the baseline K^{trans} value and $K^{trans}(t)$ is K^{trans} at time *t*.

Methods

Two baseline plus four 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} changes during the period of patient monitoring, plus inter-individual (IIV) and inter-lesion (intra-patient) (ILV) variability were described using a (modified) indirect response model, with time-varying parameters, that was augmented with an empirical time-delayed feedback loop (Figure 1). The k_i and F_i parameters in Figure 1 represent fractional (day^{-1}) and absolute (K^{trans}/day) rates of change of the K^{trans} parameter over time. The population mean parameters and interindividual variances were estimated using NONMEM. True individual baseline K^{trans} was estimated for each lesion by assuming that it varies around the observed average baseline with variance $s^2/2$ [3]. Simulated K^{trans} profiles were produced using the estimated population mean and variance parameters and empirical Bayes estimates were obtained for each patient's individual parameters.

Results

Our population model, with time delayed feedback, is able to describe the rapid decrease of K^{trans} followed by slower return to baseline within 12 days after a single dose of bev, with rebound over baseline in some patients (Figure 2). ILV in the trajectory of K^{trans} change 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 estimated parameters is identifiable and estimated to be larger for parameters in the indirect response component of the model than for the feedback component (112% CV vs. 55% CV).

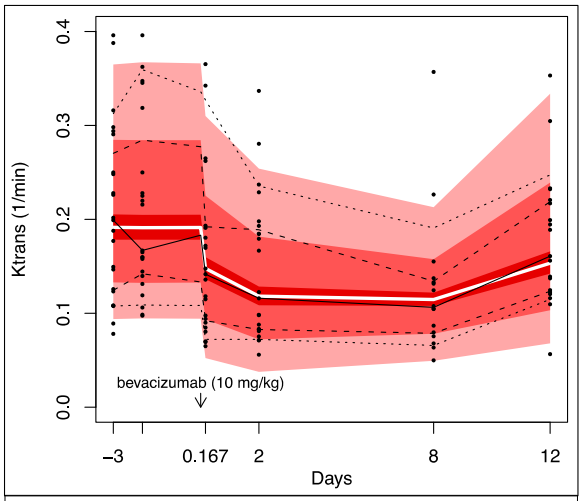

Figure 2. NONMEM simulations of fitted mixed effects model. The median (solid white line) plus 10%-90%, 25%-75% and 45%-55% quantiles of simulations are shown (shaded regions) along with observed K^{trans} values for each DCE-MRI scan (circles) [10%-90%, 25%-75% quantiles and medians of the observed values are indicated by dotted, dashed and solid black lines].

Conclusion

We have developed a mathematical model capable of describing the response of K^{trans} to a single dose of bevacizumab, characterized by rapid decrease during the first 4 hours post-dose, followed by a slower return to baseline over 12 days. For this population there is a significant amount of inter-patient variability (IIV) in K^{trans} response to a single dose of bev; inter-lesion intra-patient variability (ILV) is not detectable within these data.

References

[1] O'Connor et al. Clin Cancer Res. 2009 Nov 1;15(21):6674-82.
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[3] Port RE et al. Br J Clin Pharmacol. 1998 Nov;46(5):461-6.