Analysing within and between patient tumour heterogeneity via imaging: Vemurafenib, Dabrafenib and Trametinib in metastatic melanoma

Hitesh Mistry[1], David Orrell[2] and Raluca Eftimie[3]

[1]Manchester Pharmacy School, University of Manchester, UK;

[2]Systems Forecasting, Toronto, Canada; [3]Division of Mathematics, University of Dundee, UK

Email: hitesh.mistry@manchester.ac.uk

Overview

Objective: The aim of this study was to analyse the within and between patient variability in tumour dynamics under treatment using routinely collected clinical trial data using RECIST criterion. A key question of interest was how does within patient variability in tumour shrinkage relate to between patient.

Data: Data from the phase III studies of the three drugs mentioned was obtained through **clinicalstudydatarequest.com** Our interest was in patients who had some degree of response and so patients with only one on-treatment measurement were removed from the analysis.

Methods: A mathematical model of tumour growth based on biological understanding and empirical observations was developed and placed within a statistical population analysis framework (mixed-effects). Unfortunately in-direct comparison methods could not be used as the control treatment in these studies is not effective and so sufficient time-series is not available. Therefore quantitative conclusions are not provided but qualitative ones are.

Results/Conclusions: The results show that there is a degree of correlation in tumour size dynamics within a patient as knowing which lesion belongs to which patient considerably improved model fit to data. This led to analysis of within and between patient variability of initial tumour size and tumour shrinkage rates, both of which show differences between the Vemurafenib and Dabrafenib treated patients.

Patients & Data

Table showing the imaging characteristics of the patients used in this analysis. Note that there is no difference in terms of response between Vemurafenib and Dabrafenib.

	Vemurafenib	Dabrafenib	Trametinib
Patients			
N	203	165	157
SLD (mm)			
Median	72	62	64
(25th, 75th percentile)	(39, 122)	(34, 100)	(32, 106)
ILD (mm)			
Median	17	21	18
(25th, 75th percentile)	(10, 29)	(16, 34)	(12, 30)
ORR (CR + PR) WK6			
N	121	104	46
(%)	(60)	(63)	(29)
% Change SLD WK 6			
Median	-34	-39	-18
(25th, 75th percentile)	(-47, -21)	(-53, -22)	(-31, -4)

Data was collected using RECIST criteria. SLD: Sum of Longest Diameters, ILD: Individual Longest Diameters, ORR: Objective Response Rate, CR: Complete Response, PR: Partial Response, WK6: Week 6

Methods: Tumour Growth Model

1932

ON A LAW OF GROWTH OF JENSEN'S RAT SARCOMA

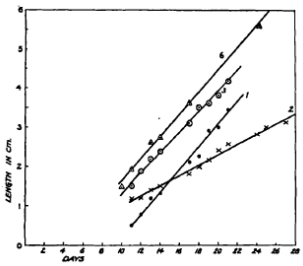
W. V. MAYNEORD, M.Sc.

The Cancer Hospital (Free), London

Quotes from paper

"The rather surprising fact emerges that the increase in long diameter of the implanted tumour follows a linear law"

"…a simple explanation of the approximate linearity in terms of structure of the sarcoma… not the whole of the mass is in a state of growth, but only a thin capsule…"



Since 1932 many others have made similar observations

Model: Derivation of Linear Law

Assume viable rim has thickness d, assumed small relative to radius r, grows rate a, volume is approximately:

$$V_p = 4\pi r^2 d$$

and it is growing at a rate

$$\frac{dV_p}{dt} = aV_p = a4\pi r^2 d$$

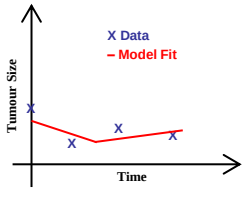
growth equation for the radius is given by

$$\frac{dr}{dt} = \frac{dr}{dV}\frac{dV}{dt} = \left(\frac{1}{4\pi r^2}\right) a4\pi r^2 d = ad$$

which is solved to give the linear equation

$$r = R_0 + adt$$

R_0 is initial radius, ad replaced by constant c.



Justification for using a piece-wise linear model for time-series analysis – nothing more!

Acknowledgements

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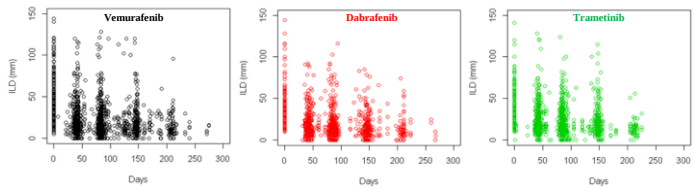
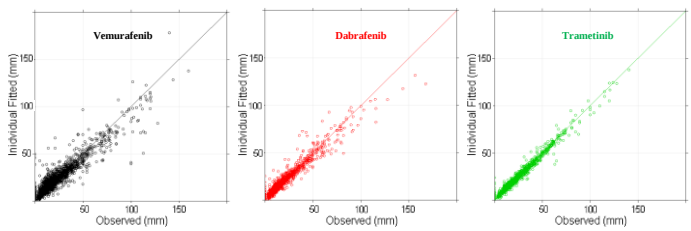
Time-Series Data and Model Fits



Above: plots showing temporal evolution of individual longest diameters (ILD).
Below: mirror plots show piece-wise linear model captures the data.



Key Results

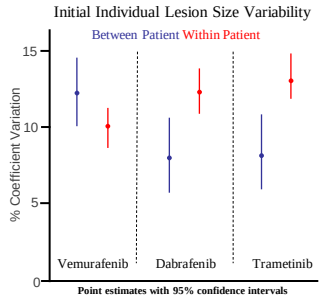
- **Knowing which lesion belongs to which patient matters**

  Null hypothesis: variability in tumour size dynamics is same between patients as it is within patients - **reject**

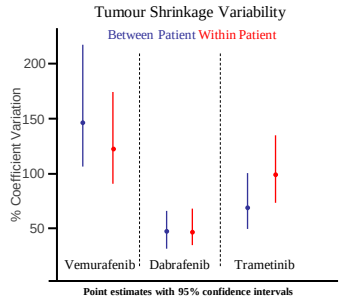
Drug	LRT p-value	Test-Statistic
Vemurafenib	<0.001	814
Dabrafenib	<0.001	64
Trametinib	<0.001	146

Likelihood ratio test (LRT)

- **Vemurafenib and Dabrafenib differentiated via variability in initial tumour size and lesion shrinkage rates**



Inference: Dabrafenib and Trametinib within patient variability is greater than between for initial lesion size – subjectivity of choice of lesion?



Inference: Greater variability in tumour shrinkage around the mean value for Vemurafenib than Dabrafenib.

Other Results

- **Tumour shrinkage does not correlate with resistance growth rate – how fast you shrink a lesion has no influence on how quickly resistance develops in that lesion**
- **Tumour shrinkage rates are an order of magnitude greater than growth rates**