PHARMACODYNAMICS

A new model

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URLs
Colon cancer
http://www.cancer.gov/cancertopics/types/colon-and-rectal

Kevin Hicks, William Wilson and colleagues have combined *in vitro* and *in vivo* data to produce a mathematical model that describes drug action as a function of the distance of the target from blood vessels. It can be used to predict anti-tumour efficacy in human tumour xenografts.

The plasma concentration of a therapeutic drug is often used as a surrogate for the concentration of the drug in the tumour. However, the disorganized nature of tumour vasculature means that drugs must diffuse over considerable distances to reach all their target cells. Poor penetration of a drug through the extravascular compartment of a tumour is therefore likely to result in therapy failure.

To better reflect this reality, the authors measured the tissue penetration properties of a hypoxia-targeted drug, tirapazamine (TPZ), that is specifically toxic to hypoxic tumour cells because it is reduced to a DNA-damaging free radical under hypoxic conditions. They measured the diffusion of TPZ using their *in vitro* 3D cell-culture model in which HT29 colon cancer cells are grown as multicellular layers. They also measured the plasma pharmacokinetics (PK; drug concentration over time) of TPZ in nude mice and the metabolism and cytotoxicity of TPZ in stirred, anoxic cultures of HT29 cells. The authors then used these data to model drug transport in a well-characterized microvascular network of a rat mammary carcinoma in which parameters such as oxygen transport and the direction and velocity of blood flow are known. Their resulting PK and pharmacodynamic (PD; effect of the drug) mathematical model predicted that the access of TPZ to the hypoxic regions of a tumour would be compromised by its diffusion and metabolic properties to the extent that the maximum number of hypoxic cells killed would be much less than if TPZ behaved in accordance with its plasma PK properties alone.

The authors validated the model by predicting and then measuring the efficacy of 15 TPZ analogues with different tumour-penetration properties. There was a strong correlation between model-predicted and actual numbers of cells killed in HT29 xenografts as determined by clonogenic assay. However, this correlation was lost if the model was based on plasma PK only.

Wilson and colleagues conclude that data from *in vitro* 3D tissue-culture models combined with PK and PD models that consider extravascular drug diffusion are useful for predicting the efficacy of drugs in tumour tissue. This might also reduce the numbers of animals required to test the initial efficacy of new chemotherapeutic drugs.

Nicola McCarthy

ORIGINAL RESEARCH PAPER Hicks, K. *et al.* Use of three-dimensional tissue cultures to model extravascular transport and predict *in vivo* activity of hypoxia-targeted anticancer drugs. *J. Natl Cancer Inst.* 16 July 2006 (doi:10.1093/jnci/djj306)
FURTHER READING Drug penetration in solid tumours. Minchinton, A. I. & Tannock, I. F. *Nature Rev. Cancer* **6**, 583–592 (2006)