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New drug leaves cancer cells gasping for air

Sharon Dorrell, Freelance writer

A new drug designed to enhance the effectiveness of radiotherapy and chemotherapy against established tumours has just entered Phase I clinical trials in the UK. AQ4N has been developed to target and kill the treatment-resistant hypoxic cells that occur in all solid tumours and contribute to treatment failure.

Hypoxic cells are highly resistant to radiotherapy and chemotherapy and act as a source of malignant cells for tumour regrowth following cancer treatment.

Laurence Patterson (School of Pharmacy, University of London, London, UK) developed AQ4N along with a group of similar compounds that are toxic to hypoxic tumour cells. Tumour angiogenesis (Box 1) is a chaotic and often incomplete process[1]. Therefore, the new blood vessels are often insufficient to meet the demands of the rapidly growing tumour and, as a result, pockets of hypoxic cells develop. The cells in close proximity to a blood vessel experience cycles of normal and poor oxygen supply, whereas those further away become chronically hypoxic[1].

It is uncertain how hypoxic cells resist radiotherapy and chemotherapy. However, Will Steward, Professor of Oncology at the University of Leicester (Leicester, UK) and principal investigator of the trial, suggests that the chemotherapy might not actually be delivered to the cells in adequate amounts because delivery relies on blood supply.

AQ4N

Once inside hypoxic tumour cells, the prodrug AQ4N is converted to its cytotoxic form, AQ4, by an enzyme-mediated reduction reaction (Fig. 1). The reaction is inhibited by oxygen, which ensures that the cytotoxin is only activated in hypoxic cells. Cytotoxic AQ4 blocks cell division by binding non-covalently to DNA and inhibiting the action of DNA topoisomerase II. Studies by Patterson and colleagues suggest that AQ4N approximately doubles the effect of a dose of radiotherapy or chemotherapy[1].

Clinical trials

'Hopefully, AQ4N will have no side-effects because it is inert and the toxic form of the drug, AQ4, will only be active in the hypoxic cancer cells,' says Steward. The safety and efficacy of the new drug will be evaluated in ongoing and forthcoming clinical trials, the first of which includes 12 patients with advanced oesophageal cancer who are undergoing radiotherapy.

The trial is taking place at two UK sites, the Leicester Royal Infirmary (Leicester, UK) and the Imperial Cancer Research Fund Unit at the Churchill Hospital

Box 1. Tumour angiogenesis

Tumour angiogenesis is an important target for new cancer treatments. Tumours create their own blood supply that not only provides them with oxygen and nutrients to grow but also a conduit for metastasis.

Tumours secrete angiogenesis activators that trigger a signalling cascade to stimulate local vascular endothelial-cell growth. Activators include a variety of proteins, including vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (FGF) among others, and small molecules, such as adenosine and prostaglandins E1 and E2. Tumours also secrete matrix metalloproteinases (MMPs) to break down the tissue matrix and enable endothelial cells to migrate and form new blood vessels.

Several angiogenesis inhibitors are currently at various stages of clinical evaluation in the treatment of cancers (http://www.html:/cancertrials.nci.nih.gov/news). Their mechanisms of action include:

- blocking matrix breakdown
- inhibiting endothelial cells directly
- blocking angiogenesis activation
- inhibiting endothelial-specific integrin and/or survival signalling
- a non-specific mechanism of action.

Angiogenesis inhibitors work exclusively to inhibit blood vessel growth and are unlikely to reduce tumour size in patients with advanced disease[a]. They are, therefore, most likely to be of use in the early stages of tumour growth. Moreover, as vascular endothelial cells only divide approximately once every three years (see website), inhibitors of the process are unlikely to be toxic, although they are useful when given concomitantly with chemotherapy or radiotherapy, both of which produce unpleasant side-effects.

Other new developments to block tumour blood-supply include a new drug from Aventis (Parsippany, NJ, USA) called AVE8062, which targets existing tumour blood-supply and, like AQ4N, might be of use in patients with advanced cancer.

a Herbst, R.S. *et al*. (2001) Clinical studies of angiogenesis inhibitors: the University of Texas MD Anderson Center trial of human endostatin. *Curr. Oncol. Rep.* 3, 131–140

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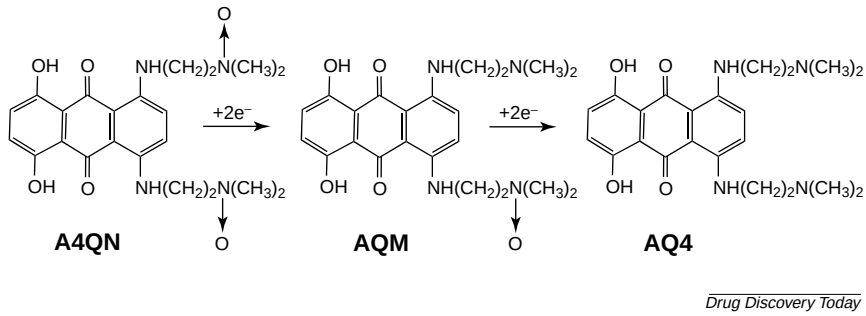

Figure 1. AQ4N undergoes bioreduction to produce the toxic AQ4 (Ref. 1). AQ4 is 1,4-*bis*[{2-dimethylaminoethyl}-amino]5,8-dihydroxyanthracene-9,10-dione. AQ4N is the di-*N*-oxide of AQ4.

(Oxford, UK). In the first instance, AQ4N is being given in conjunction with standard radiotherapy. 'The drug has the potential to reduce the radiation dose and side-effects, but the main reason for its use is to kill more cells,' explains Steward. Each patient receives two intravenous injections of AQ4N; one dose 14 days before radiotherapy and another immediately beforehand. Steward anticipates that the trial will run for 6–12 months. Further preliminary trials that examine the use of AQ4N in conjunction with chemotherapy and its dosage are also being planned. If AQ4N is successful Steward believes that it will be commercially available in 3–4 years.

Reference

1 Patterson, L.H. and McKeown, S.R. (2000) AQ4N: a new approach to hypoxia-activated cancer chemotherapy. *Br. J. Cancer* 83, 1589–1593

Depleting cholesterol to make sex safer

Martina Habeck, Freelance writer

Researchers have discovered that removing cholesterol from cell membranes inhibits the infectious ability of HIV. They hope that β-cyclodextrins (BCD), which can deplete cells of cholesterol, could provide a new microbicide for use against sexual transmission of the disease.

HIV begins its infection by binding to the CD4 receptor and to a co-receptor (chemokine receptor sites CCR5 or CXCR4) on the host-cell surface. Attachment to the receptor and co-receptor enables HIV to fuse with the host-cell membrane and to empty its contents into the cell so that it can replicate. The virus can also spread to other cells through fusion of an infected cell with an uninfected cell (Fig. 1). When newly formed virus particles bud from the surface of the host cell, they take a part of the host-cell membrane with them to form the viral envelope.

Lipid rafts

The HIV envelope excludes CD45, a highly expressed leukocyte surface protein, whereas it incorporates other host membrane-proteins that are far less abundant. In an attempt to explain this phenomenon, James Hildreth and his team at Johns Hopkins University School of Medicine (Baltimore, MD, USA) proposed that HIV-1 budding does not occur at random membrane sites, but at specific regions known as lipid rafts, which also exclude CD45 (Box 1). Confocal fluorescence microscopy and virus phenotyping using monoclonal antibodies supported their hypothesis, demonstrating that lipid-raft-associated molecules, such as the glycosylphosphatidylinositol (GPI)-linked proteins Thy-1 and CD59 and the ganglioside GM1, are incorporated in the viral envelope, whereas molecules specific for other membrane regions are excluded[1].

Encouraged by their findings, the scientists investigated whether lipid rafts are involved in other aspects of HIV-1 biology. Lipid rafts are particularly rich in cholesterol, which is important for many biological functions, including fusion.

Box 1. Lipid rafts

Cell membranes contain ordered microdomains enriched with glycosphingolipids and cholesterol. These lipid assemblies are thought to form so-called rafts that serve as moving platforms for a variety of cellular events, such as membrane trafficking, signalling and cell adhesion[a]. Rafts exert their function by separating or concentrating specific membrane-proteins. Among the molecules included in lipid rafts are glycosylphosphatidylinositol (GPI)-linked proteins, whereas molecules such as the membrane phosphatase CD45 or cadherin E are excluded.

a Simons, K. *et al.* (1997) Functional rafts in cell membranes. *Nature* 387, 569–572

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