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Targeted taxane therapy for cancer

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Several new modifications to the best-selling anticancer drug paclitaxel (Taxol™) could significantly increase the dose of the drug that can be used. The goal is to target delivery more precisely to the tumour, thereby reducing side effects and enabling higher doses to be administered at equivalent toxicity levels.

Paclitaxel is an anti-mitotic agent that prevents cell division by interacting with tubulin, the protein from which microtubules are made. As cells prepare to divide, microtubules assemble through the polymerization of tubulin dimers. When division is complete the tubulin depolymerizes and the microtubules disappear. Paclitaxel and other taxanes work by binding to the β-tubulin component of the dimer, promoting microtubule assembly but inhibiting breakdown [1]. The cell becomes choked with microtubules, can no longer divide and consequently dies.

The taxanes are the most effective drugs currently available against breast cancer [2]. Paclitaxel is also approved for the treatment of advanced ovarian cancer, non-small-cell lung cancer and Kaposi's sarcoma. However, as with other chemotherapy agents, side effects limit the dose that can be used. As well as hair loss, nausea and vomiting, side effects include joint and muscle pain, peripheral neuropathy and bone marrow suppression, which can lead to severe anaemia and/or neutropenia and increased susceptibility to infection. Severe allergic reactions occur in 2–4% of patients (http://www.taxol.com). Some of these are thought to be a result of Cremophor EL (polyoxyethylated castor oil), which is used as a vehicle for paclitaxel because of the drug's extremely lipophilic nature [3].

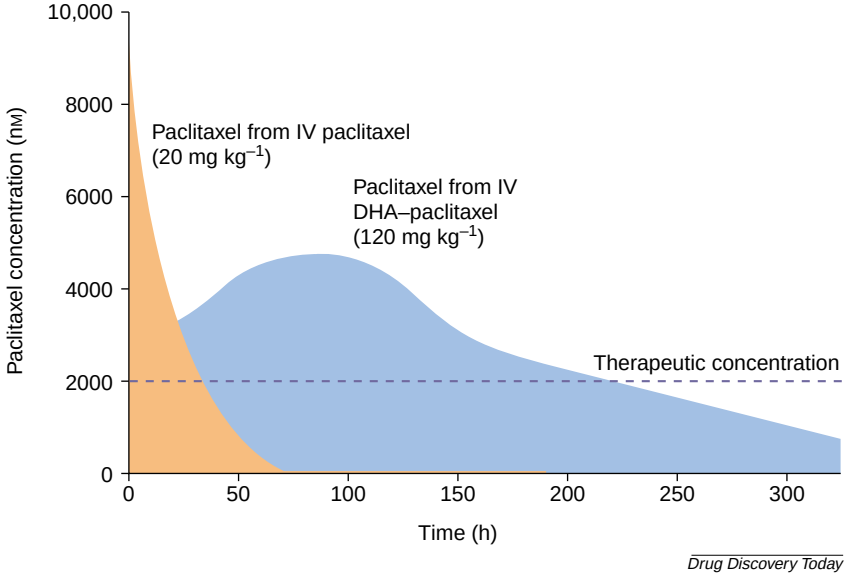

Figure 1. Concentrations of paclitaxel in M109 tumours following single intravenous 120 mg kg^{-1} doses of docosahexaenoic acid (DHA)–paclitaxel or paclitaxel in mice. The therapeutic concentration of paclitaxel is only maintained for a short period, whereas the therapeutic concentration of DHA–paclitaxel is sustained for longer.

DHA–paclitaxel

In an attempt to reduce these side effects, Protarga (King of Prussia, PA, USA) has conjugated paclitaxel to docosahexaenoic acid (DHA), a natural fatty acid that is readily taken up by tumour cells. The conjugate appears not to be cytotoxic until the bond with DHA is cleaved within the cell. The maximum safe dose in humans is 4.6-fold higher than the maximum approved paclitaxel dose, and patients in a Phase I study experienced few side effects [4].

'This is not targeting in the sense that the drug goes only to tumour cells,' says Matthews Bradley of Protarga. 'However, we are seeing tumour targeting as we define it, that is, you get more of the drug accumulating in tumours when it has the fatty acid attached than you do without it.'

In M109 tumour-bearing mice, DHA–paclitaxel showed superior antitumour activity to paclitaxel, completely eliminating the tumours in 100% of mice when administered for five days at optimum dose [5] . DHA–paclitaxel produced an area under the drug concentration–time curve that was eightfold greater than that produced by paclitaxel at equimolar doses and 57-fold greater at equitoxic doses [5]. This means that therapeutic concentrations of drug are maintained in tumours for extended periods (240 h) after administration (Fig. 1). During this time, many quiescent cells that would be missed by short-acting doses will enter cell division and be killed.

'It is possible that our drug might have a wider activity against different tumours than paclitaxel because having more drug in tumours for a longer period of time suggests that you might get more activity,' says Bradley. Phase II studies of the product, Taxoprexin®

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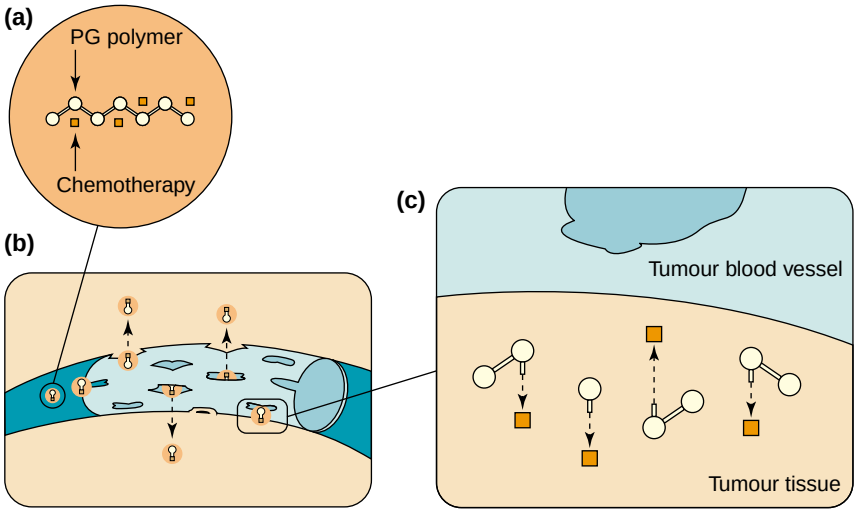

Figure 2. Polyglutamate (PG) technology and selective delivery of tumour-killing drug. When linked with PG **(a)**, cancer killing drugs such as paclitaxel circulate in the bloodstream, pass through the leaky tumour blood vessel wall and become trapped in the tumour tissue **(b)**. Because the tumour vessels are more permeable to PG compared with vessels in normal tissue, significantly higher levels of chemotherapy drug accumulate in the tumour. Inside the tumour, PG is cleaved and the cytotoxic drug is released **(c)**.

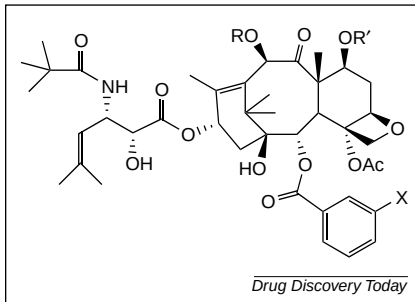

Figure 3. Generalized structure of the new class of highly potent taxanes developed by ImmunoGen (Cambridge, MA, USA).

(DHA–paclitaxel), are under way in breast, prostate and six other cancers.

PG–paclitaxel

An alternative approach, being developed by Cell Therapeutics (Seattle, WA, USA), is to link paclitaxel to a polyglutamate (PG) polymer. This exploits the fact that tumour blood vessels have leaky endothelial membranes that are porous to molecules such as PG, whereas normal blood vessels are not. Again, preclinical data suggests that the drug concentration achieved within the tumour is higher than with free paclitaxel. Normal organs are exposed only to the conjugated form, which is water soluble, stable until taken up by cells and non-cytotoxic *in vitro* [6]. The mechanism of action is shown in Figure 2.

Phase I/II trials are being carried out in patients with recurrent or advanced cancers who have failed other treatments. Few of these patients usually respond to further treatment, and they often experience severe side effects. However, preliminary results show that PG–paclitaxel (CT2103) is well tolerated; side effects are mild and no dose-limiting toxicities have been reported at doses equivalent to standard paclitaxel doses.

There have been some encouraging tumour responses: 'In our ovarian cancer study we were pleasantly surprised to see partial responses in patients who actually had resistant disease and had failed Taxol therapy within the past six months,' says Carolyn Paradise from Cell Therapeutics. 'We have some evidence that this could be because the PG–paclitaxel is probably metabolized to a monomeric form within the cell,' she explains. 'This could then bypass the mechanism that pumps free paclitaxel out of the cell again, allowing the concentration to build up. Ultimately it is probably broken down to the free drug, but in close proximity to where it has to work.'

Tumour-activated prodrugs

ImmunoGen (Cambridge, MA, USA) has recently applied taxanes to its Tumor-Activated Prodrug (TAP™) technology, in which drug molecules are attached to tumour-specific monoclonal antibodies (mAbs). The conjugated form is selectively taken up by the targeted tumour, and again is only activated once inside the cell. In the past, the use of antibodies to target drugs has given disappointing results in human trials. Premature drug release reduced the targeting precision, and it was impossible to get high enough drug concentrations into the tumour [7]. 'Drugs delivered by immunoconjugates need to be active at concentrations in the range of 10^{-10} M,' explains Walter Blättler of Immunogen, 'Our taxane derivatives are significantly more potent than paclitaxel or docetaxel. In mice, the taxane-based TAP (Fig. 3) completely eradicated human tumour xenografts at non-toxic doses [8].

Two TAP drugs have entered clinical trials, to date, both using the maytansinoid chemotherapy agent DM1. So far, the technology is working as expected. 'We have been able to give patients much higher doses than are possible with free maytansin,' says Blättler. 'We have not seen the classic toxicities found with maytansin; the drug is indeed behaving like a conjugated maytansin prodrug.' No date has been set yet for clinical trials of taxane TAPs.

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