Protecting the genome

There is no direct evidence that gene damage from chemotherapy causes adverse health effects. But with the growing population of ALL survivors, the oldest of whom are in their mid- to late-twenties, the issue is increasingly important. 'We need to ensure that these children can live long lives without later effects,' says Finette. 'There may be other drugs we can give simultaneously to minimize the damage. I hope a lot of other people will now start looking at this; maybe we can develop drugs that will protect the genome.'

This could already be a step closer. Stephen Lipschultz and colleagues at Dana-Farber Cancer Institute (http://www.dfci.harvard.edu) have just published a study [2] showing that dexrazoxane, an established heart drug that scavenges for free radicals, reduced the incidence of heart damage from 50% to 25% when given simultaneously with doxorubicin to children with ALL.

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New generation leukaemia drugs are on their way

Laura Nelson, lauranels@yahoo.co.uk

Since Gleevec was introduced as the leukaemia wonder-drug, its success has been tarnished by resistance in patients. Second-generation leukaemia drugs, which target the same protein as Gleevec but in a different way, might offer relief to Gleevec-resistant patients.

Resistance to Gleevec arises from mutations in the target protein, which prevent binding of the drug. 'The second-generation drugs bind mutant molecules to which Gleevec doesn't bind,' says John Goldman, Professor of Leukaemia Biology and Therapeutics at Imperial College London (http://www.ic.ac.uk). 'They appear to have a wider spectrum of affinity,' Goldman says.

Wonder drug

Gleevec (imatinib), approved by the US Food and Drug Administration (FDA) in 2001, was the first of its kind to treat chronic myeloid leukaemia (CML), which affects 1 in 10,000 people each year in the USA.

Ninety-five percent of patients respond to Gleevec in the early stage of leukaemia, but after a year 11% are resistant, according to Neil Shah, an oncologist at the David Geffen School of Medicine at the University of California, Los Angeles (http://dgsom.healthsciences.ucla.edu), who tested a new leukaemia drug, called BMS-3548251.

Shah says: 'It's premature to say BMS-354825 is better than Gleevec. But we're optimistic in the clinical data we've seen so far.' The first patients enrolled in a Phase I clinical trial for the new drug in November 2003 and the data will be presented in December 2004. BMS-354825 was supplied by Bristol-Myers Squibb (http://www.bms.com).

Preventing overactivity

Leukaemia drugs target a protein that is involved in the pathogenesis of CML, an enzyme called Abelson tyrosine kinase (ABL). In CML, ABL becomes overactivated and initiates the growth of cancer cells. Gleevec works by binding to ABL in its inactive form, preventing it from becoming active [2].

The causes of Gleevec resistance are mutations in the tyrosine kinase that stops the drug from binding. There are 17 known mutations that underlie resistance, either altering the protein at the drug binding site or preventing the enzyme from adopting the inactive conformation [3].

Less selective: more effective

The new leukaemia drugs, which include BMS-354825, also target ABL. But they appear able to bind to mutated forms of the protein. Shah found that BMS-354825 was effective at treating CML in mice and worked against 14 of 15 Gleevec-resistant forms

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of the protein. Without treatment, mice died from leukaemia within 15 days, while all treated animals remained healthy. BMS-354825 also slowed the proliferation of cultured bone marrow cells isolated from patients with leukaemia.

Shah says that it is too early to predict whether resistance will occur with the new drug over time but, as it probably has fewer binding requirements than Gleevec, it might be less susceptible to resistance, he says.

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Private prescription:

A thought-provoking tonic on the lighter side

Column by **Raymond C. Rowe**, AstraZeneca, UK

Please note that these are the personal opinions of the author and do not necessarily represent those of AstraZeneca.

Hard to swallow!

On 3 August 1962, Malcolm Muggeridge (1903–1990), the British author and journalist, wrote in *The New Statesman* [1]:

'I will lift mine eyes unto the pills. Almost everyone takes them, from the humble aspirin to the multi-coloured, king-sized three deckers, which put you to sleep, wake you up, stimulate and soothe you all in one. It's an age of pills.'

Of course, Muggeridge was not referring to pills as such because the process used to manufacture them was unable to produce a three-layered formulation. Indeed, he was writing about the compressed tablet, a product that has, over the past 50 years, consistently 'topped the polls' in its popularity as a drug delivery system. Indeed, recent surveys [2,3] have shown that tablets account for over 30% of the dosage forms used for new medical entities in the USA and over 40% of formulations manufactured in the UK. However, both pills and tablets have a common feature in that they must be swallowed by the patient before the drug that they contain can exert its pharmacological effect. Nothing unusual about that, you might think, but the pattern of pill or tablet taking can, and does, vary from patient to patient. The diversity observed in the idiosyncrasies of patients when taking their tablets prompted a nurse, Cindy LaRue, to publish her findings [4].

Swallowing tablets

In her article, LaRue identifies several broad patient categories depending on their 'pill-taking patterns'. Using LaRue's definitions, plus a couple or so of my own, the characteristics of the different pill-taking patterns are described below.

Shot-glass downers

LaRue defines this technique as simply 'down the hatch'. The patient takes the receptacle of tablets and, irrespective of the quantity, throws the head back and empties the contents into the mouth in one quick motion. A mouthful of water quickly follows and everything is swallowed in one gulp.

Dry swallowers

As the name suggests, these patients simply swallow their tablets without any liquid. As an aside, LaRue describes these patients as unassuming and usually over 40 years of age. LaRue writes that initially she was confident that they were not swallowing their medication but storing it in their cheeks before spitting it out after she had left.

Tongue flippers

LaRue describes this intricate procedure in detail as follows:

'The pill [tablet] is placed on the roof of the mouth behind the front teeth. The water is then taken into the mouth, with the tongue remaining in position and put at the back of the throat ready to swallow. The pill [tablet] is then catapulted into the water with the

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