Professor of Neurology and Director of the Center for Aging and Developmental Biology at Rochester.

Although this study was performed in mice and not in humans, it shows that a level of control over the immune response to an AD vaccine can be attained and paves the way for a brighter future for those suffering from this disease.

References

1 Bowers, W.J. *et al.* (2004) HSV amplicon-mediated Aβ vaccination in Tg2576 mice: differential antigen-specific immune responses. *Neurobiol. Aging* (in press)
2 Schenk, D. *et al.* (1999) Immunization with amyloid-β attenuates Alzheimer-disease-like pathology in the PDAPP mouse. *Nature* 400, 173–177
3 Orgogozo, J.M. *et al.* (2003) Subacute meningoencephalitis in a subset of patients with AD after Aβ42 immunization. *Neurology* 61, 46–54

Surprise at genotoxicity findings for childhood leukaemia therapy

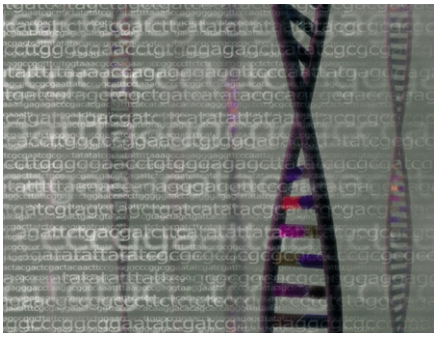
Jo Whelan, Freelance Writer

Children who survive acute lymphocytic leukaemia (ALL) thanks to standard chemotherapy are left with higher than expected rates of genetic damage, researchers have found. Chemotherapy is so successful that almost 80% of children with ALL now survive at least five years. However, the powerful antineoplastic drugs damage normal as well as cancerous cells, in some cases leading to organ damage and leaving survivors with a 5–20-times greater risk of developing secondary cancers in later life.

Barry Finette and colleagues at the University of Vermont, Burlington (http://www.uvm.edu), analyzed 130 blood samples from 45 children on standard treatment protocols for ALL, starting at first diagnosis and continuing during, and for five years after, treatment [1]. To measure the genotoxic effect of the drugs they looked at the frequency of somatic mutations in the *HPRT*-reporter gene, a widely used biomarker for mutation rate.

Surprise mutations

They found that the number of mutations carried by the children rose



during each phase of therapy, culminating in a 200-fold increase on completion. This is between 10 and 100 times higher than the increases in *HPRT* somatic mutation frequency recorded in survivors of nuclear bombs and workers involved in the cleanup of Chernobyl, and is thought to be the greatest increase ever recorded after exposure to genotoxins. Furthermore, the mutation frequency failed to drop back in the years after treatment, instead remaining high and increasing at the normal age-related rate.

'We were surprised at the degree of the increase, and at the fact that the mutation frequency remained elevated after cessation of treatment,' says Finette. The few studies done in adults exposed to genotoxins have shown a decrease in mutation frequency once exposure ends. He believes the increase found in the children is real: 'We've been doing this [measurement] for years with hundreds of patients,' Finette says. 'We don't believe it's an artefact.' Nor do they think that the treatment simply selects for existing cells with *HPRT* mutations.

However, Alan Kinniburgh, Senior Vice President for Research at the Leukemia and Lymphoma Society in the USA (http://www.leukemia.org), is cautious about the high numbers of mutations recorded. 'A selection effect by chemotherapy on HPRT mutations cannot be ruled out,' he says. 'But this does not detract from the finding that [these] therapies are mutagenic, and that this is the most likely explanation for the increased incidence of secondary malignancies.'

Another surprising finding, Finette says, was that the increase in mutation frequency was the same whether the children were on low-intensity or high-intensity regimens, despite significant differences in the respective dosages and clinical toxicity involved.

1359-6446/04/$ – see front matter PII: S1359-6446(04)03228-3

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.

References

1 Rice S.C. *et al.* (2004) Genotoxicity of therapeutic intervention in children with acute lymphocytic leukaemia. *Cancer* Res. 64, 4464–4471

2 Lipschultz S.E. *et al.* (2004) The effect of dexrazoxane on myocardial injury in doxorubicin-treated children with acute lymphocytic leukaemia. *New Engl. J. Med.* 351, 135–153

New generation leukaemia drugs are on their way

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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

PII: S1359-6446(04)03229-5