TRIAL WATCH

Immunotherapy boost

A cancer vaccine designed to stimulate an immune response against the tumour antigens carcinoembryonic antigen (CEA) and mucin 1 (MUC1) has entered a Phase III clinical trial for the treatment of patients with metastatic pancreatic cancer.

The vaccine, called PANVAC-VF, was developed by Therion Biologics Corporation. It includes recombinant vaccinia and fowlpox viruses that co-express CEA and MUC1, which are expressed by over 90% of pancreatic tumour cells. The vaccine also incorporates the costimulatory molecules B7.1, ICAM1 and LFA to enhance and sustain the antitumour immune response.

In Phase I studies of 22 patients with advanced pancreatic cancer, 20 of whom had metastatic disease, vaccination with PANVAC-VF resulted in a median overall survival of 7.9 months and at least 5.3 months. This is in comparison to an anticipated median overall survival of approximately 3 months, based on historical controls. The most common adverse event was a reaction at the injection site, but no serious side effects were observed.

A multicentre, randomized, controlled Phase III trial is underway, enrolling 250 patients with advanced pancreatic cancer who have not responded to treatment with gemcitabine. The primary end point will be overall survival, compared with palliative chemotherapy or best supportive care. The study will also determine safety, quality of life, change in serum tumour antigen levels, response rate and disease stabilization.

Immunotherapies targeted at CEA and MUC1 have also been tested in patients with other tumours that are known to overexpress the CEA and MUC1 antigens, including breast, lung and colorectal cancers. Therion and the National Cancer Institute are now planning up to 18 additional studies with PANVAC-VF in patients with these cancers.

ORIGINAL RESEARCH PAPER Schuetz, T. *et al.* Two phase I studies of prime-boost vaccinations with vaccinia-fowlpox vaccines expressing CEA, MUC-1, and TRICOM costimulatory molecules (B7.1/ICAM-1/LFA-3) in patients with advanced pancreatic cancer. *Am. Soc. Clin. Oncol. abstract 2564* (2004)

Cardiotoxicity reduced

A novel anthracycline, pixantrone, has been given fast-track status by the Food and Drug Administration for relapsed, aggressive non-Hodgkin's lymphoma. Anthracyclines, such as doxorubicin, are part of standard treatment for non-Hodgkin's lymphoma together with cyclophosphamide, vincristine and prednisone (CHOP). However, anthracyclines are associated with cumulative heart damage that limits their use in patients previously treated with anthracyclines and prohibits their use in many others.

Pixantrone (made by Cell Therapeutics Inc.) is easier to administer than doxorubicin and has not shown the same risk of cardiac damage. The drug design was based on the anthracycline mitoxantrone — the OH groups thought to cause free-radical production and cardiotoxicity were removed and replaced with nitrogen. The molecule is still planar, so the substitution does not effect intercalation into DNA, where the drug causes its damage.

Cell Therapeutics tested single-agent pixantrone in 30 patients with aggressive non-Hodgkin's lymphoma who had already received 300 mg/m² doxorubicin, which would normally make them ineligible for further anthracycline treatment. Five patients had a complete response and four had a partial response; responses lasted an average of 11 months. Pixantrone is now being studied in combination, replacing doxorubicin in CHOP, and preliminary results of 22 patients have shown 13 with complete responses and four with partial responses. Pixantrone was well tolerated, with neutropaenia as the dose-limiting toxicity.

Other trials, including a Phase II trial of pixantrone with rituximab in relapsed indolent non-Hodgkin's lymphoma, are ongoing.

WEB SITE http://www.cticseattle.com/prod_frame-iprod-pix.htm

TUMOUR SUPPRESSORS

A guardian and a suppressor

There are some fundamental processes in biology that we would expect to be conserved across all species. And yet some of them use a surprising variety of molecular mechanisms. A recent report by McPherson *et al.* shows that the MUS81 endonuclease, which is involved in processing branched DNA structures in yeast, such as those found in stalled replication forks, is required in mammals for genomic stability and tumour suppression.

To clarify the role of *Mus81* *in vivo*, the authors knocked out the gene in mice. Based on the role of Mus81 in yeast, they expected the mice to show meiotic recombination defects, such as infertility. To their surprise, the animals were fertile with no defects in gametogenesis. Normal gene targeting in the *Mus81*^{-/-} embryonic-stem-cell lineage, and B- and T-cell lineages (the ontogeny of which requires DNA rearrangements), confirmed that *Mus81* is not required for a cell to cope with double-stranded DNA breaks.

But *Mus81* knockout mice do have a phenotype — mutant embryonic stem cells are hypersensitive to the alkylating agent mitomycin C, indicating that the gene might be involved in repairing mitomycin-C-induced DNA interstrand crosslinks. *Mus81* also seems to act as a haploinsufficient genome caretaker — loss of even one copy of *Mus81* leads to aneuploidy and other chromosomal defects.

Although, at first glance, mutant mice seem to be normal, the authors found that only 27% of homozygotes and 50% of heterozygotes were healthy and survived through their first year. Many had tumours, mainly non-Hodgkin's lymphomas, that at the cellular level were associated with aneuploidy. Because *Mus81* homozygotes and heterozygotes were equally susceptible to cancer, both copies of *Mus81* must be required for its tumour-suppressor function — just as two copies are required for genome integrity.

Although MUS81 is not alone in being a haploinsufficient tumour suppressor, it is at odds with the common view that tumorigenesis requires the loss of both copies of a tumour suppressor. Mechanistically speaking, the genomic instability caused by *Mus81* haploinsufficiency might facilitate tumorigenesis, for example, in preneoplastic lymphocytes. However, it remains to be seen whether the model that the authors propose is correct — that is, that a 50% reduction in the amount of MUS81 protein in heterozygotes is not sufficient to resolve intermediate DNA structures that form during DNA repair.

Magdalena Skipper
Editor, Nature Reviews Genetics

References and links

ORIGINAL RESEARCH PAPER McPherson, J. P. *et al.* Involvement of mammalian Mus81 in genome integrity and tumour suppression. *Science* **304**, 1822–1826 (2004)