TRIAL WATCH

SMART? Time will tell

The UK-based biopharmaceutical company Antisoma has completed recruitment for a multicentre randomized Phase III trial of pemtumomab in ovarian cancer — patients will receive either standard treatment alone or standard treatment plus pemtumomab as adjuvant therapy. A total of 420 patients have been enrolled into the SMART (study of monoclonal antibody radioimmunotherapy) trial, and the primary end point is survival. Interim results of the SMART trial will be available at the end of 2003 and the trial will be completed in late 2004.

The 5-year survival rates for ovarian cancer treated with standard therapy — surgery plus chemotherapy, such as a platinum agent and a taxane — are about 30%. Pemtumomab (formerly Theragyn or HMFG1) is a mouse monoclonal antibody conjugated to the radioisotope yttrium-90 that binds specifically to a glycoform of the MUC1 mucin. This protein is overexpressed on the surface of epithelial tumour cells, including ovarian, gastric, breast and lung.

The Imperial Cancer Research Fund (now Cancer Research UK), from whom pemtumomab is licensed, carried out a Phase II study in women with advanced ovarian cancer. Of the 21 women who were in remission at the time of treatment with the antibody, 15 responded well and 14 of these 21 patients were still alive more than 8 years after treatment. The eligibility criteria for the SMART trial — patients must have no visible evidence of residual or recurrent disease at second-look laparoscopy — is based on the subgroup that was shown to benefit in the Phase II trial.

Treatment with a single intraperitoneal dose of pemtumomab is thought to target and destroy residual disease, thereby preventing or delaying relapse. About 65% of patients with newly diagnosed ovarian cancer could be eligible for pemtumomab treatment.

Smokers wanted

The National Cancer Institute has launched a US $200 million study to determine if either spiral computerized tomography (CT) or chest X-ray screening reduces deaths from lung cancer. The National Lung Screening Trial (NLST) will enroll 50,000 current or former smokers and will take place at 30 sites throughout the United States. The randomized, controlled study is scheduled to last until 2009. Trial participants must be between the ages of 55 and 74, and they will receive either a chest X-ray or a spiral CT once a year for three years.

Spiral CT uses X-rays to scan the entire chest in about 15–25 seconds. It can detect tumours that are less than 1 cm in size, whereas chest X-rays detect tumours that are about 1–2 cm in size. Many hospitals have begun performing spiral CT scans of smokers and former smokers to detect small tumours, although no scientific evidence has shown that early detection can actually save lives.

Recent studies indicate that 25–60% of CT scans of smokers and former smokers will show abnormalities. Most of these abnormalities, however, are not lung cancer, as the lungs of smokers typically contain many scars, areas of inflammation or other noncancerous conditions that can mimic lung cancer. The trial is therefore controversial, as some patients could be placed at risk of receiving unnecessary biopsies, surgery, radiotherapy or chemotherapy.

Early detection techniques are desperately needed, however, as lung cancer is the leading cause of cancer-related deaths in the United States. An estimated 90 million current and former smokers are at high risk for developing the disease, and by the time lung cancer is detected, it has already metastasized in 15–30% of cases.

WEB SITE National Lung Screening Trial Questions and Answers:
http://newscenter.cancer.gov/pressreleases/NLSTQA.html

ONCOGENESIS

MYC reduces stress

The list of accomplishments on MYC's resumé continues to grow, as Yuzuru Shiio *et al.* report in *EMBO Journal* that increased expression of MYC reduces the level of actin stress fibres and focal adhesions within cells, which could influence their ability to invade and metastasize.

The authors analysed global protein expression using isotope-coded affinity-tag reagent labelling and tandem mass spectrometry in two rat cell lines — Myc(–), in which c-*Myc* is deleted, and Myc(+), which is the same cell line but with c-*Myc* reintroduced. Myc is present in Myc(+) cells at ~fivefold the level of that in wild-type cells. This is within the range of Myc expression that is found in tumour-derived cell lines.

Of the 528 proteins analysed, 177 had at least a twofold expression difference between the two cell lines. Functionally related groups tended to have similar expression patterns; for example, adhesion molecules, actin-binding proteins and Rho pathway proteins, which might influence cell morphology and adhesion, were downregulated in Myc(+) cells, and those involved in protein synthesis and anabolism, which would influence cell growth, were upregulated in Myc(+) cells.

The link between Myc and cell growth has been made before, and is strengthened by Myc's ability to regulate genes that are important in this; however, a link between Myc and cell morphology has not. To investigate this further, the authors performed immunofluorescence on Myc(–) and Myc(+) cells, and found that Myc(+) cells possessed fewer focal adhesions and actin stress fibres. This was shown to be due to a decrease in signalling from the Rho pathway, and introduction of a hyperactive RhoA into Myc(+) cells significantly restored the actin stress fibres.

Expression of Myc in mouse NIH-3T3 cells also results in a reduction of actin stress fibres and focal adhesions, but this does not seem to be caused by decreased expression of RhoA. Instead, levels of Cdc42 — a Rho protein family member — and actin are reduced.

So, this proteomic analysis has revealed yet another potential function for Myc in tumorigenesis. By reducing adhesion and increasing motility, Myc might promote invasion and metastasis.

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References and links

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FURTHER READING Pelengaris, S. *et al*. c-MYC: more than just a matter of life and death. *Nature Rev. Cancer* **2**, 764–776 (2002)
WEB SITES
Ruedi Aebersold's lab:
http://www.systemsbiology.org/research/faculty/Ruedi_Aebersold.html
Robert Eisenman's lab: http://expertise.cos.com/cgi-bin/exp.cgi?id=441228