TRIAL WATCH

Fast track for breast cancer drug

The United States Food and Drug Administration (FDA) has granted fast-track designation for Arimadex (anastrozole), which has been in clinical trials for post-menopausal women with early-onset breast cancer. This decision follows quickly after the release of data last month from the ATAC (Arimadex, tamoxifen, alone or in combination) study — the largest adjuvant breast cancer trial ever conducted. The ATAC study involved 9,366 patients with early-onset breast cancer who had completed surgery and chemotherapy and were candidates for adjuvant hormonal therapy. Researchers found that a significantly lower number of women in the Arimadex group had a relapse or died, compared with women who received tamoxifen. Arimadex already has FDA approval for treatment of post-menopausal women with locally advanced or metastatic breast cancer that is oestrogen-receptor positive or of unknown receptor status, and also for treatment of advanced breast cancer that has failed tamoxifen therapy in post-menopausal women. Tamoxifen, which competes with oestradiol for binding to oestrogen receptors, has been used for over 20 years to treat breast cancer. Arimadex has a slightly different mechanism from tamoxifen in that it inhibits oestrogen synthesis.

WEB SITE: www.astrazeneca-us.com

The good, the bad and the ugly

The results of two chemotherapy trials published in the *New England Journal of Medicine* bring mixed news for lung cancer patients. First, the good news: in a Phase II trial of 154 patients, Kazumasa Noda and colleagues found that, compared with the current standard of care (etoposide plus cisplatin), combining the topoisomerase I inhibitor irinotecan with cisplatin vastly increased the survival of patients with metastatic small-cell lung cancer — one of the most aggressive forms of cancer. This combination increased the percentage of patients surviving for two years or more from 5.2% to 19.5%.

But the situation is much less clear cut for patients with metastatic non-small-cell lung cancer. Several agents, including gemcitabine, docetaxel and paclitaxel, have shown promising results in combination with a platinum drug (cisplatin or carboplatin), but which combination is the most effective? Joan Schiller and colleagues aimed to find out in a trial of over 1,200 patients, but they discovered that all of these therapies give a similar response rate, with a median survival of just 8 months.

In an accompanying editorial, Desmond Carney makes a strong case for giving up on trying to improve chemotherapy regimens, favouring the development of therapies that are based on the biology of the disease, as well as prevention strategies and screening. "The current treatment…is nonspecific, nonselective and toxic. New combinations of chemotherapy are not likely to make substantial improvements in survival", he says.

ORIGINAL RESEARCH PAPERS Noda, K. *et al.* Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N. Engl. J. Med.* **346**, 85–91 (2002) | Schiller, J. H. *et al.* Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N. Engl. J. Med.* **346**, 92–98 (2002)
FURTHER READING Carney, D. N. Lung cancer — time to move on from chemotherapy. *N. Engl. J. Med.* **346**, 126–128 (2002)

GENETICS

Balancing act

Susceptibility to prostate cancer commonly runs in families and has a large hereditary component, but despite numerous linkage studies and whole-genome scans, the genes responsible have eluded us. Now, a consortium of researchers from the United States, Finland and Sweden seem to be closing in on a suceptibility target. They report that mutations in a tumour-suppressor gene can be linked to hereditary prostate cancer (HPC).

In the February issue of *Nature Genetics*, Carpten *et al.* examined a region on chromosome 1, known as *HPC1*, that had been previously identified as a prostate cancer susceptibility locus. In analysing candidate genes in this region, they found that mutations in a gene encoding ribonuclease L (*RNASEL*) were carried by members of two separate HPC families. In one family, a heterozygous mutation introduced a premature stop codon into the *RNASEL* gene, whereas in the other family a heterozygous mutation disrupted the initiation codon. Most importantly, all the male family members who carried these mutations eventually developed prostate cancer.

Analysis of tumour DNA from one of these men revealed loss of heterozygosity — cancer cells had managed to delete the remaining wild-type copy of the gene. Accordingly, no RNase L protein could be detected in tumour cells. Low levels of protein were expressed in non-cancerous epithelial cells of these individuals, presumably from the remaining wild-type allele. RNase L therefore seems to function as a tumour suppressor. Previous studies showing that RNase L activity is completely lost in hepatoma cell lines support this conclusion.

So what is the exact role of RNase L in normal prostate function and during tumorigenesis? Mice deficient in this protein have defects in interferon-induced apoptosis and antiviral responses, indicating that it might be involved in regulating cell survival. Prostate cells are known to walk a fine (hormonally regulated) line between cell proliferation and death. The authors speculate that loss of function of one protein in either of these pathways is enough to tip a cell's balance from death towards proliferation — which might be enough to initiate tumorigenesis.

Carpten *et al.* suggest that this gene might someday be useful in early prostate cancer diagnosis. Other *RNASEL* mutations, however, must be identified in additional groups of men with prostate cancer to confirm that this is a *bona fide* susceptibility gene.

Kristine Novak

References and links

ORIGINAL RESEARCH PAPER Carpten, J. *et al.* Germline mutations in the ribonuclease L gene in families showing linkage with *HPC1*. *Nature Genet.* **30**, 181–184 (2002)
FURTHER READING Feldman, B. J. & Feldman, D. The development of androgen-independent prostate cancer. *Nature Rev. Cancer* **1**, 34–45 (2001)
WEB SITE
Jeffrey Trent's lab: http://www.nhgri.nih.gov/Intramural_research/People/trent.html