ELSEVIER

European Journal of Cancer 40 (2004) 309–313

European Journal of Cancer

www.ejconline.com

NEWS. . .NEWS. . .NEWS

Time for a paradigm shift in cervical cancer?

HPV (human papillomavirus) testing could become the first line of screening for cervical cancer, with cytology reserved for women who test positive, UK researchers suggest (*Lancet* 2003; 362: 1871–1876). They confirm that HPV testing is more sensitive primary screening tool for high-grade carcinoma among women aged 30 and above.

Rather than adding HPV testing to cytology, the team, led by Professor Jack Cuzick at Cancer Research UK, suggest it could be used alone as an initial test. Although currently more expensive than cytology, costs "are certain to drop for high volume use in primary screening," they say. If HPV testing safely permits longer screening intervals, costs would be further reduced.

"CERVICAL CANCER IS CAUSED BY A SEXUALLY TRANSMITTED VIRUS"

The HART (HPV in Addition to Routine Testing) study included 11,085 women aged 30–60 years, attending family practices for routine cervical screening. They received both conventional cytology and an HPV test. HPV testing was more sensitive than borderline or worse cytology (97% vs 76%), but less specific (93% vs 95%), for detecting high grade CIN.

Certain types of HPV "are the primary cause of almost all cases of cervical cancer," the researchers say. An efficient policy for the management of those with a positive test for HPV but negative or borderline cytology will be necessary for HPV testing to become a cost-effective, routine screening tool, they say. The HART study found that, among these women, surveillance at 12 months was as effective as immediate colposcopy. More than one in 3 were HPV-negative at 12 months.

They suggest a new approach to cervical screening "in which the primary screening test would be for HPV alone and cytology would be reserved for the triage of women with positive HPV test results."

Other issues remain. "The use of HPV testing reinforces the fact that cervical cancer is caused by a sexually transmitted virus, and it will be essential for the test result and its implications to be communicated sensitively," they write.

An accompanying editorial notes that the average sensitivity of the Pap smear to detect cervical cancer precursors is 51%. The high false-negative rate is its "most critical limitation," states Dr Eduardo Franco (McGill University, Montreal, Quebec, Canada). "False negative diagnoses have important public-health and legal implications; the latter being a serious problem in the USA", he writes (*Lancet* 2003; 362: 1866–1867).

He calls for cervical cancer prevention to be guided by evidence from well-conceived randomised controlled trials. "Oddly enough," except for a few trials of triage, "there have been no published randomised trials of HPV testing in population screening," he writes.

"TEST RESULTS MUST BE COMMUNICATED SENSITIVELY"

The HART's study suggestion that only those who test positive for HPV should be screened with cytology is "truly provocative", but may well be correct, Dr Franco says. "The Hart trial can be viewed as a launching pad for future randomised trials that will assess the duration of protection conferred by a negative HPV result and the efficacy of a Pap-centred triage approach."

This changes the current morphology-based approach to one in which the search for a sexually transmitted virus becomes the focus of disease detection. "Clients and providers will have to learn to live with the new paradigm, one which places the emphasis of prevention not only on women but on their partners as well. It is about time," he concludes.

Fast track for nelarabine

The US' Food and Drug Administration (FDA) has granted fast track status to nelarabine. It applies to the treatment of T-cell acute lymphoblastic leukaemia and lymphoblastic lymphoma among patients who have not responded to or whose disease has progressed during treatment with at least 2 standard regimes.

Nelarabine is a nucleoside analogue rapidly converted to arabinosylguanine nucleotide triphosphate, resulting in inhibition of DNA synthesis and cytotoxicity. Early clinical work shows activity in aggressive T-cell malignancies.

The designation follows promising results from a phase II study, presented at the 45th annual meeting of the American Society of Hematology (ASH). The Children's Oncology Group (COG) study was sponsored by the National Cancer Institute (NCI) under a clinical trials agreement between NCI and GlaxoSmithKline. The drug is not currently approved for the treatment of any disease in any country.

EJC News is compiled by:
Helen Saul
Tel.: +44 (0)1865 843340
Fax: +44 (0)1865 843965
E-mail address: h.saul@elsevier.co.uk

0959-8049/$ - see front matter
doi:10.1016/j.ejca.2003.12.010

COX-2 expression distinguishes stomach and oesophagus

Use of selective COX-2 inhibitors in the treatment of adenocarcinomas of the gastric cardia is less promising than in Barrett cancers, Dutch researchers say. The adenocarcinomas are often considered as one clinical entity, but the researchers found significant differences in COX-2 expression (*Gut* 2003; **52**: 1678–1683).

They examined tumour sections from 306 consecutive patients undergoing potentially curative surgery for an adenocarcinoma of the oesophagus, gastro oesophageal junction and gastric cardia (invading the distal oesophagus). They found significantly lower COX-2 expression in the adenocarcinomas of the gastric cardia, than in Barrett's carcinomas.

"COX-2 EXPRESSION IS NOT PROGNOSTIC IN GASTRIC CARDIA"

In cancers of the gastric cardia, COX-2 expression did not correlate with any clinicopathological parameter. There was no correlation between elevated COX-2 expression and reduced survival, as has been described for Barrett carcinomas. In previous work, the group, from the Academic Medical Centre, Amsterdam, the Netherlands, demonstrated that elevated COX-2 expression is an independent prognostic variable for Barrett carcinomas (*Gastroenterology* 2002: **122**: 1800–1807).

"DIFFERENT TUMOURS REQUIRE DIFFERENT TREATMENT STRATEGIES"

Adenocarcinomas of the gastric cardia and distal oesophagus are at present often considered as one clinical entity because of their comparable increasing incidence, prognosis and optimal treatment options. However, the researchers from write, "It is questionable whether these two carcinomas have the same molecular characteristics."

The researchers say that the pattern of expression may help explain the discrepancy. In cardia carcinomas, the strongest COX-2 expression is in the invading peripheral margin of the tumour. In Barrett carcinoma, expression was homogenous. "This suggests that in cardia carcinomas, COX-2 upregulation is a relatively late event and occurs in invasive malignant cells that are often already infiltrating the lymphatic system or blood vessels, which could explain why COX-2 expression is not a prognostic factor."

Another possibility is that elevated expression of COX-2 is only a prognostic variable for poor prognosis in relatively early carcinomas. Patients with Barrett carcinoma in this series had significantly more favourable T and N stages than those with cardia cancers.

The role of selective COX-2 inhibitors in prevention and treatment of gastrointestinal cancers is "promising", the researchers say, but "further investigations are needed before they can be incorporated into daily clinical practice. This study demonstrates that different tumours may require different treatment strategies."

New treatment hope for prostate cancer

Early studies that combine a vaccine against prostate-specific antigen (PSA) with the cytotoxic drug docetaxel are showing promise for the treatment of prostate cancer.

"This second-generation vaccine showed immunogenic activity and slowed tumour progression", said Philip M Arlen, National Cancer Institute, MD, USA. "However, we still want to determine whether. . .we can prolong the time to progression and improve survival."

Arlen presented his findings at the International Conference on Molecular Targets and Cancer Therapeutics, Boston, MA, USA (17–21 Nov, 2003). The vaccine consists of a recombinant vaccinia virus that expresses the *PSA* gene, and a recombinant virus that expresses the B7·1 costimulatory gene. Treatment also consists of a sequential monthly booster vaccine of recombinant fowlpox virus containing the *PSA* gene.

All 26 patients studied (aged between 51 and 85 years) presented with androgen-independent metastatic prostate cancer. They received 100 mg of granulocyte-macrophage colony-stimulating factor for 4 days with each vaccination. The investigators then randomised the patients to receive either the vaccine plus weekly docetaxel and pretreatment with dexamethasone (13 patients), or vaccine alone (13 patients). The treatment cycle lasted for three consecutive weeks followed by a 1 week pause. Patients in the group receiving vaccine whose disease progressed were switched to weekly docetaxel therapy.

For patients receiving the combination therapy, treatment lasted about 103 days. For those receiving single therapy—including patients who were switched to docetaxel because their disease progressed—treatment lasted about 180.5 days.

Of the 26 patients originally enrolled in the study, 15 are still taking part, including eight of 13 patients in the combination group. Two patients have had a confirmed decline in PSA that exceeds 50%, and one patient has had a partial response.

"The main question the study addressed was whether the addition of steroids with chemotherapy is going to affect responses to vaccine", comments Arkadiusz Dudek, University of Minnesota, Minneapolis, USA.

"Typically we don't want patients on any type of steroids while they're receiving immunomodulation", he adds, noting oncologists' concerns that T-cells may receive apoptotic signals from the steroids. However, stresses Dudek, "This study suggests that is not the case. This small study gives some assurance that we shouldn't fear using chemotherapy agents that require steroids along with [vaccines]".

Paula Moyer

"Bystander effect" may improve radiotherapy

The so-called "bystander effect", which may be harnessed to enhance radiotherapy in future, is mediated, at least in part, by nitric oxide (NO), researchers say (*Cancer Research* 2003; **63**: 23). If mechanisms underpinning the effect can be controlled, "potential new approaches may be developed to improve the efficiency of radiation treatment," they say.

The finding contributes to understanding of the bystander effect, by which—contrary to the established view—radiation kills many more cells than are hit directly. It now appears that cells hit directly by radiation release signals which prompt apoptosis among neighbouring cells.

Scientists from Cancer Research UK's Gray Cancer Institute (Middlesex, UK) were among the first to develop the single-cell microbeam, which fires a beam of helium ions a thousandth of a millimetre wide. They used one of only 2 fully operational in the world in the current study.

Human glioblastoma T98G cell nuclei were individually irradiated with an exact number of helium ions. When only 1 cell in a population of 1200 was targeted, significant cellular damage was measured in neighbouring unirradiated cells. When up to 20% of cells were individually targeted, the micronuclei yield—a measure of cell death—greatly exceeded that predicted when all of the cells were targeted assuming no bystander effect.

However, when a NO-specific scavenger was present in the culture medium, the micronuclei yields reduced to the predicted values. This "indicates that NO contributes to the bystander effect," the researchers wrote.

Dr Kevin Prise, who led the Cancer Research UK work, said, "Our discovery has important implications both for optimising the effectiveness of radiotherapy and for protecting healthy tissue from its effects. If we could enhance the bystander effect within tumours, we could develop much more effective systems of radiotherapy, perhaps using lower doses to reduce side effects. But of course it also means that even very low doses of radiation may be doing more damage to normal cells than we'd thought, so we'll have to look for ways of protecting healthy tissue more effectively."

He said that high amounts of the NO produced within tumours may be essential to optimise the bystander effect and improve treatments. "The mechanisms involved in the bystander effect might be different in healthy and cancerous tissue, so it might be possible to develop drugs that protect normal tissue from radiotherapy while leaving cancer cells more vulnerable."

Down's syndrome gives clues to cancer genes

The unusual profile of solid tumours among children with Down's syndrome (DS) hints that oncogenes and tumour-suppressor genes are located on chromosome 21, French researchers say (*Pediatric Hematology and Oncology* 2003; **20**: 517–529).

They collected all cases of malignant solid tumours observed in DS patients aged up to 19 years within the network of the Société Française d'Oncologie Pédiatrique (SFOP). Between 1980 and 2001, only 21 cases were identified. However, the distribution was peculiar: a lack of intracranial tumours and embryonal neoplasms combined with an over-representation of lymphomas and germ cell tumours.

The authors say their study is the largest ever published on the topic. The rarity of solid tumours has already been noted. The 21 cases correspond to nearly 1 annual case of solid tumour among around 50,000 people with Down's syndrome under 20 years living in France.

The general under representation masks more complex variations: germ cell tumours, haematopoietic solid tumours and retinoblastoma seem over represented, while brain tumours and embryonal neoplasms are decreased.

It is probably that chromosome 21 harbours both oncogenes and tumour-suppressor genes over expressed through gene dosage effect and interacting in a complex manner. "A good knowledge of the tumour profile of DS will be an important help in identifying genes relevant for oncogenesis and understanding the process of carcinogenesis in the general population," the researchers conclude.

Heart problems linked with 5-FU

The incidence of angina pectoris in patients on 5-fluorouracil treatment may be higher than previously suspected, say German researchers (*Oncology* 2003; **65**: 108–112). "Attentiveness to these symptoms and immediate treatment are crucial," they write.

They followed 102 consecutive and unselected patients treated with 5-FU, and found that almost 1 in 5 developed reversible symptoms of angina pectoris during treatment. Symptoms lasted up to 12 h after cessation of the infusion.

The researchers say that it is possible that the unexpectedly high rate of chest pain occurred because patients knew they were participating in a study of cardiac function. However, most of the patients complaining of angina pectoris showed corresponding ECG changes. In 6 of the patients investigated with coronary angiography, none showed coronary artery disease.

Symptoms could be relieved by calcium antagonists and the researchers hypothesise that they are caused by a reversible vasospasm. Antivasospastic therapy is the first approach, they say. Careful surveillance beyond the half-life of 5-FU is "mandatory", they say, as symptoms and ECG changes last up to 12 hours after discontinuation of 5-FU.

"Clinical and ECG manifestation of angina should prompt drug discontinuation. Whether reexposure to the triggering drug is safe remains to be answered in another controlled trial," they conclude.

Highlights from San Antonio Breast Cancer Symposium (Texas, USA, 3–6 December 2003)

ErbB inhibitor shows promise

GW 572016, a reversible inhibitor of ErbB1 and ErbB2, has been granted fast track status by the US' Food and Drug Administration (FDA) for the treatment of certain patients with refractory advanced or metastatic breast cancer who have failed previous therapies. It follows promising early results from a clinical study, including women with advanced breast cancer.

14 of 26 women who took the drug for at least 8 weeks showed either a partial response or disease stabilization. Most of this group were refractory to trastuzumab therapy, which targets the ErbB2 pathway. The drug was shown to hit the ErbB1 and ErbB2 targets and the results are "encouraging", according to manufacturer GlaxoSmithKline.

Letrozole "does not impair" quality of life

New data on the MA-17 trial provided reassurance that the aromatase inhibitor letrozole (Femara) can be taken in the extended adjuvant setting without adversely influencing quality of life.

The recently reported MA-17 study (*NEJM* 2003: **349**: 19) was conducted in Belgium, Canada and the States and involved researchers from European Organisation for Research and Treatment of Cancer (EORTC). It showed that letrozole significantly improved disease-free survival. It almost halved the risk of local or metastatic recurrence or new primary contralateral cancers. Independent investigators stopped the study after the first interim analysis to amend the protocol to give all subjects the opportunity to take letrozole.

The study involved 5187 postmenopausal women who had taken tamoxifen for five years. Half were given letrozole and the remainder placebo. Nearly two and a half years later, women taking letrozole were 43% less likely to relapse or develop a new contralateral cancer.

The quality of life data presented at San Antonio reviewed eight domains of quality of life—physical health, role function, bodily pain, general health, vitality, social function, and mental health - by questioning participants at the start of the study and on subsequent visits. The study, in 3582 women, found that the deterioration in scores with time was similar in both groups for five of the domains, and only marginally worse for women taking letrozole in three of the domains. In bodily pain 63% showed deterioration on letrozole opposed to 58% on placebo; for general health 60% showed deterioration on letrozole opposed to 57% on placebo and for vitality 68% on letrozole opposed to 63% on placebo.

"This was of borderline statistical significance and showed that the effect on quality of life of taking letrozole was much lower than many oncologists had predicted," says lead investigator Dr Paul Goss from the Princess Margaret Hospital, Toronto, Canada. "Since both arms were so similar it demonstrates that women in general experience many symptoms in day to day life that can't be attributed to medical interventions."

Neoadjuvant anastrozole "reduces mastectomies"

Preoperative treatment with anastrozole may reduce tumour volume and enable breast-conserving surgery (BCS) in patients previously thought to be only eligible for mastectomy, researchers say.

Results from the IMPACT1 (Immediate Preoperative Arimidex, Tamoxifen or Combined with Tamoxifen) trial involved 330 postmenopausal women with hormone-sensitive, operable, breast cancer. Of 124 initially scheduled to have a mastectomy, pre-treatment with anastrozole enabled more women to undergo BCS than treatment with tamoxifen. BCS became feasible in twice as many women treated with anastrozole as those treated with tamoxifen (46% versus 22%).

Both drugs were generally well tolerated.

IMPACT trial investigator, Professor Ian Smith (Royal Marsden Hospital, London, UK) said "The IMPACT data add to the increasing body of evidence supporting the use of anastrozole in treating patients prior to surgery... The benefit anastrozole appears to have in this setting is very promising, particularly when compared with tamoxifen."

Iressa in Advanced breast cancer

Gefitinib (Iressa) is showing activity in the treatment of advanced breast cancer, researchers say. In a phase II open-label trial, 68 patients received oral gefitinib in combination with paclitaxel and carboplatin as first-line treatment. A clinical response was observed in 63% of patients (complete response 14%, partial response 49%).

Dr Alan Barge (AstraZeneca) said, "A number of clinical trials with gefitinib in advanced breast cancer, both as monotherapy and in combination with hormonal or cytotoxic agents have been initiated. These trials include the measurement of specific biomarkers before and after treatment to help identify those types of patients most likely to benefit from gefitinib."

Tamoxifen's role in question

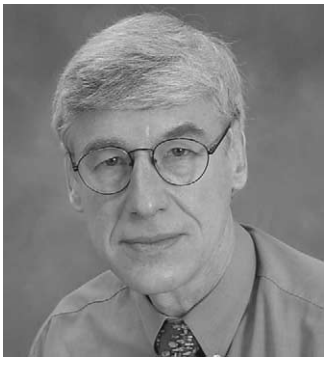
Tamoxifen's role as standard adjuvant therapy for postmenopausal women with hormone-sensitive early breast cancer is again challenged following new data from the ITA (Italian Tamoxifen Anastrozole) Trial.

The data suggest that patients who switch from tamoxifen to anastrozole after 2–3 years' therapy are less likely to experience a relapse than those who remain on tamoxifen for the full 5 years. It appears to reinforce the findings of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) study, which have already shown anastrozole to be a more effective treatment with an overall more favourable tolerability profile for newly diagnosed postmenopausal women with early breast cancer.

PODIUM

The Importance of Evaluating Evidence

Professor Ian Tannock is the Daniel E Bergsagel Professor of Medical Oncology at Princess Margaret Hospital and University of Toronto, Canada. He studied at Cambridge and London Universities, UK, and completed his medical training at the University of Pennsylvania, USA. He has won numerous awards for his work and gave a Plenary lecture on 'Cancer clinical trials—the key to improving outcome' at ECCO - 12, 2003.



Professor Ian Tannock

How good are we at evaluating evidence?
We are improving. Organisations like the Cochrane Collaboration have focused attention on evidence-based medicine. Many professionals can put data in perspective according to whether it is derived from randomised controlled trials (RCTs) at one end of the spectrum of evidence, or a case series at the other. Organisations which draw up guidelines, such as those in the States, Canada and France, apply levels of evidence to the available data and are helping us to think more critically.

What are the problems in drawing up guidelines?
Sometimes the most needed trials do not exist. Many trials are industry-sponsored and although some are relevant and well done, others are designed to support a product rather than to expand knowledge. Further, although large RCTs tend to be performed more rigorously than smaller trials because more people are involved, which means more checks and balances, some may be of poor quality. Trials need to be properly evaluated and, of course, they must be published. In a recent study (*JAMA* 2003; **290**: 495–501), we found that of RCTs presented at ASCO, 1 in 4 had not been published 5 years later. There is still a strong bias for positive trials to be published earlier than negative ones. Some large negative trials are never published.

Why?
Mostly because investigators lose interest, run out of time or can't be bothered, which to some extent is unethical. Patients agree to take part in trials on the understanding that they are contributing to science. You are breaking your contract with them if you do not publish.

Does a delay in itself cause a bias?
Yes. Suppose 5 trials are set up to address a question, and one, by chance, gives a positive result. Its apparently impressive results are published rapidly, often in a high impact journal. If the 4 negative trials are not published at all, or only after a delay, the literature is unbalanced.

Most advances in oncology are relatively small and there is always a chance of a false positive result. In general, unless a result is sufficiently large and convincing, treatment approaches should only be changed after a confirmatory trial. An apparent improvement of 5–10% in survival can occur by chance alone.

Would a registry of ongoing trials help?
It would. Publicly-funded trials tend to be registered, and the Cochrane Collaboration tries to obtain data from all sources, whether published or not, but of course can only include the unpublished sources that are known. A more complete registration process would be a step forward.

Are the trials themselves improving?
Yes, but some published trials do not present data in the fairest way. In reading a report it's important to question a trial's internal validity: whether it is well-designed, whether the stated endpoints are appropriate and meaningful to patients, how randomisation was achieved, whether analysis was appropriate, with all patients accounted for, and whether the primary endpoint was used to draw the main conclusion. Its external validity hangs on how the results fit in with the rest of the literature. For example, if 10 trials show a most minimal benefit when chemotherapy is added to local treatment, but one shows a large benefit, it is likely to be an artefactual result.

Are there particularly desirable features of oncology trials?
When possible, they should be large. If you're asking a question about long-term survival or cure in a common disease like breast, lung or colorectal cancer, a difference of 3–4% between 2 regimens could translate into increased survival for 100s or 1000s of patients. You need about 4000 patients to detect or rule out a difference of 5%.

Do you have reservations about very large trials?
Sometimes large trials detect small transient differences in survival. The key question is whether a small temporary gain is worth putting thousands of patients through chemotherapy with its associated toxicity and potential to impair quality of life, if benefits are small.

How can doctors hope to keep up with the literature?
Even though the literature is vast, the development of guidelines, overviews of clinical trials and computer-based databases is making it easier to access the evidence.

How do you see things changing in future?
Young oncologists need a strong education in clinical trial design and analysis so that they can read the literature critically. They also need to be able to work with industry while remaining critical. Young investigators need to avoid conflict of interest and to separate their own goals from those of the companies that sponsor trials.