



NEWS...NEWS...NEWS

CME Online — Your views, please!

FECS has launched three interactive multidisciplinary case studies on-line. It is a pilot project aimed at assessing oncologists' interest in this type of continuing medical education (CME).

The case studies are the result of collaboration between the Leonardo da Vinci partners and focus, initially at least, on medical oncology, radiation oncology and surgical oncology.

The pilot is supported by the European Commission Leonardo da Vinci programme and will run from June to December 2003. An evaluation will be made towards the end of the year. Should the pilot project generate sufficient enthusiasm and support among the

oncology community, FECS will consider pursuing this activity and have new multidisciplinary case studies regularly posted on the web. In due course, FECS will also seek to submit the cases to the Accreditation Council of Oncology in Europe (ACOE), which is in the process of developing a policy on the accreditation of distance learning programmes.

Therefore FECS calls on all oncologists to run through the case studies on the website www.FECSET.org and provide their views.

*For more information, please contact:
Ms Françoise Van Hemelryck, Project
Manager, FECS. Tel.: + 32-2-775-02
03; fax: + 32-2-775-02-00; e-mail:
francoise@fec.be*

Safety of sentinel node procedures

The injecting and imaging necessary to localise the sentinel node should be performed the day before surgery, say UK researchers (*British Journal of Radiology*, 2003, **76**, 117–122). Compared with the day of surgery, it gives lower radiation doses to staff, lower activity in excised specimens and waste, and provides a higher count rate giving better image quality, they say.

The study was preformed to assess the hazards and risks at all stages of the localisation procedure. It found that radiation doses are low and no additional procedures are required for protection of staff, provided the usual procedures for biohazards are in place.

Whole body doses were not likely to cause a problem should a member of staff be pregnant. The survey sug-

gested minimal risk to pregnant pathology or nursing staff particularly if surgery takes place on the day after injection. Female surgeons are also unlikely to receive significant doses "but the situation may require careful consideration if the same-day protocol is followed," they say.

Whole body doses to theatre and pathology staff "are significantly lower from next-day cases compared with those from same-day cases. This is largely because the level of activity in the tumour has decayed significantly over four half lives," the researchers wrote. "From radiation protection considerations, surgery on the date after dose administration and imaging is preferred," they concluded. "This is in keeping with the 'as low as reasonably achievable' principles of doses."

Cancer incidence in Flanders

New figures from the Flemish Cancer Registry Network have been published. *Kankerincidentie in Vlaanderen 1997–1999* includes data on 81,814 new cancers of all types, estimated to be around 95% of the cancers incident in the region.

Dr Elizabeth Van Eycken, Co-ordinator of the Network, said that the incidence of most cancers appeared to rise during the period because of improving registration methods. However, the incidence of lung cancer in men decreased year on year. "We have to be careful with trends because we only have 4 years of data. However, we concluded that there was a lower incidence of lung cancer in men."

Among men, the incidence of breast cancer, non-Hodgkin's lymphoma, prostate cancer and lung cancer seems to be one of the highest in Europe (source: EUCAN). More average rates were found for most other cancers.

The Flemish Cancer Registry Network has been collecting data since 1996, and the 2000 data is expected to be published in summer, 2003.

Kankerincidentie in Vlaanderen 1997–1999 is published by Flemish League against Cancer ISBN: D/2002/9738/1. Further information from Elizabeth. Vaneycken@kankerregister.org

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

Apoptosis and the age-related increase in cancer

A reduction in apoptosis “may play a significant role in the age-related increase in cancer”, UK researchers say (*British Journal of Cancer* 2003, **88**, 487–490). Apoptotic response declined with increasing age in those with and without cancer. Further, breast cancer patients showed reduced responses compared with normal controls.

Previous work from the same group showed that peripheral blood lymphocytes from those with a germ line *TP53* mutation have a dramatically reduced apoptotic response to radiation. The current study excluded those with this mutation, and included 75 normal controls, 243 breast cancer patients (72 of whom had *BRCA1* or *BRCA2* mutations) and 80 members of cancer-prone families,

who had not themselves had cancer.

Blood samples were taken and peripheral blood lymphocytes extracted and analysed. Mean apoptotic response reduced with increasing age in all groups: breast cancer cases and those with a family history of cancer but also in the unrelated control group. The odds ratio for breast cancer in women with an apoptotic response less than 35%, compared with women with a response of more than 49% was 6.42.

The age distribution of breast cancer incidence is traditionally attributed to the need for several rate-limiting somatic mutational events to occur to generate a malignant tumour. According to this model, carcinogenesis slows down at the menopause

because of the lower mitotic rate in postmenopausal women.

An alternative model (*Nature Genetics* 2000, 26, 411–414) proposed that a woman's breast cancer incidence rises sharply to a high constant rate at a genetically determined age. The authors of the *BJC* study say that systemic failure of DNA repair processes, including apoptosis, might be one of the mechanisms behind such a model.

Laboratory work has previously shown a similar reduction in apoptotic response with age in rodents. The *BJC* authors say their data “further support the hypothesis that a reduction in apoptotic response to a DNA damage with increasing age may play a significant role in the age-related increase in cancer.”

Metastasis gene in liver cancer

US and Chinese scientists have identified a pattern of gene activity, which may help predict which hepatocellular cancers will metastasise (*Nature Medicine*, 2003, **9**:4, 416–423). They also found that the osteopontin gene may be a useful diagnostic marker for metastasis.

The scientists, from the US' National Cancer Institute and the Institute of Fudan University in Shanghai, set out to identify genes which will discriminate between the original tumour and metastases in patients with hepatocellular cancer. Surprisingly, they found that the genes expressed in metastatic tumours were identical to those in the original tumour. This finding challenges the current model of metastasis progression. The researchers found, instead, differences between the activity of genes in tumours that went on to metastasise and those in tumours that did not.

“The fact that gene activity in metastatic tumours is identical to that in

the tumours from which they originated, but metastasis-free tumours are distinct, suggests that changes favouring metastasis occur in the original tumour,” said Dr Xin Wei Wang (NCI Center for Cancer Research), lead investigator of the study. “If we can identify in advance patients whose tumours are likely to metastasise, it will improve our ability to individualise treatment of their disease.”

Researchers used DNA micro array technology to examine tumour samples. They analysed the activity of 9000 genes within tumour cells, and a computer algorithm established that the activity of 153 of these genes differed significantly depending on whether or not a tumour had the potential to spread.

They then used these genes to see if they could correctly identify 40 tumour samples. The test correctly identified 82 percent of tumours which went on to metastasise, and 67 percent of those which did not.

Further analysis of these key genes identified one, which produces the protein osteopontin, whose activity was particularly high in tumours with metastatic potential. Increased activity of the gene leads to an abnormally high level of osteopontin protein in tumour cells, which appears to promote metastasis: high levels of osteopontin made cancer cells in culture more likely to invade neighbouring tissue. Conversely, blocking the activity of the protein prevented tumour cells from spreading, both in mice and in culture.

Osteopontin has some useful characteristics, which may help in the development of treatment and diagnostic tests. The protein is located on the outside of cells, meaning it may be more easily reached by pharmaceutical agents than targets inside. Further, “Osteopontin can be found in all body fluids, which makes it an excellent diagnostic marker,” said Dr Wang.

‘Distinct genetics’ of Scots and Northern Irish

The Scots and Northern Irish are genetically distinct from elsewhere in the UK and have a different legacy of inherited cancers, researchers say (*British Journal of Cancer*, 2003, **88**:8, 1256–1262). Families have inherited a distinct cluster of genetic mutations

responsible for breast cancer, including one which may have been brought over by the Vikings.

Researchers studied *BRCA* mutations in families visiting genetic clinics in Edinburgh, Glasgow, Aberdeen, Dundee and Belfast. They found 107

families, accounting for 550 cases of breast or ovarian cancer. Just 10 types of genetic damage, 5 in each gene, accounted for almost half of all the mutations detected. This is a much narrower spread than in England or Wales.

EUROFILE

New measures to halt brain drain

"More and more researchers trained in Europe leave for and remain in the USA," said Research Commissioner Philippe Busquin recently. He was speaking at a conference in Brussels in March, which looked at ways of raising European investment in research to 3% of gross domestic product. That will mean the EU having to find an extra 500 000 researchers.

Busquin announced that nearly 10% of the overall budget of the 6th Research Framework Programme has been earmarked for training, mobility and career development of researchers. The considerable losses to the USA

has dropped to below 25% in some countries, including traditional 'science nations' such as the Netherlands and Britain.

A more recent Eurobarometer looked at attitudes to science in the candidate countries, and found a slightly brighter picture. But unless salaries and conditions change, can one really expect the well-trained, talented scientists from Poland, Hungary and the Czech Republic to stay in underpaid academic research when they could find better paid jobs in business or finance?

It will not be easy to effect change in these circumstances, but Busquin is making a valiant effort. After all, his dream of a European Research Area will fall pretty flat if there is no one prepared to work in it.

The Commission's Marie Curie scheme is to fund the initial training of researchers starting their careers, either through trans-national research projects or through better-structured training in a more university-oriented

are intended to provide exhaustive information and local assistance for researchers involved in mobility with regard to any question concerning establishing themselves and staying in their host country.

Finally, under the Science and Society action plan, launched in 2002, the Commission intends to promote better communication of the results of research among the wider public and propose a more citizen-friendly science policy. A call for expressions of interest under this action plan has just been launched.

Perhaps the most high-profile example of a Europe to US brain drain is in the cancer field. Nobel Prize-winning Sir Paul Nurse, Cancer Research UK Chief Executive, recently announced that he is to leave the year-old cancer charity to become President of Rockefeller University. Although many believed that the brain drain from the UK to the US was at least slowing down, research by the campaigning group Save British Science showed that this belief was ill founded (*Nature* 2000, **407**: 13, Correspondence).

Of the 770 scientists in their sample—those who obtained a doctorate in a science subject from a UK university in 1988—only 252 were still publishing in scientific journals in 2000; a 33% continuation rate. Of the 252 tracked, 62% had recently published from a UK address, 17% from the US and 21% from elsewhere.

This is not, of course, proof of a brain drain, say the authors. 'A scientist is more than the sum of his publications'. But the analysis so far, they conclude, does show that brain drain is a serious issue.

"To achieve the EU's objectives for this decade there is an urgent need to upgrade the profession and the conditions under which research is conducted," says Busquin. "The European Research Area will not really see the light of day until it is also a European area for researchers."

Mary Rice
Brussels

ONLY 33% OF SCIENCE PhDs CONTINUE TO PUBLISH

in terms of human resources are a drain on European research resources, he said. "They reflect the lack of attractiveness and social recognition characteristic in Europe of the profession of researcher".

In relative terms, the EU produces more science PhDs than the US, but has fewer researchers (5.36 per thousand of the working population in the EU compared with 8.66 in the USA and 9.72 in Japan). The proportion of women researchers is only 29% of the total in Europe. Because many PhDs are leaving research, or leaving Europe, recruiting may soon become a national problem, says Knut Fagri, from the University of Oslo, who recently chaired an EU expert group which benchmarked human resources in research.

The Eurobarometer study carried out across in the EU in December 2001 provides some of the reasons for this sorry state of affairs. Of the young people questioned, 67.3% thought that science lessons were not sufficiently attractive; 42.4% thought career prospects were insufficient; and 40% believed that salaries were not sufficiently attractive. You do not have to look far to find the results of these beliefs — the proportion of students taking university courses in science

'THERE IS AN URGENT NEED TO UPGRADE THE PROFESSION'

environment. Another initiative concerns individual grants to meet the additional training needs of researchers who already have professional experience.

Also planned are measures concerning the transfer of knowledge to the EU's less-favoured regions and the candidate countries, both in the academic sector and industry. New instruments are being designed to encourage the creation of research teams, establish university chairs and promote the return of researchers and their professional integration.

Later in 2003, the Commission, in co-operation with the Member States and associated countries, will launch a European portal for the mobility of researchers and a European network of mobility centres. These initiatives

Millions of women 'could benefit from tamoxifen'

In the US alone, 2 million women would have a net benefit from taking tamoxifen for breast cancer chemoprevention, researchers say (*JNCI* 2003, **95**:7, 526–532). More than 28,000 breast cancers could be prevented or deferred, they say.

The US Breast Cancer Prevention Trial previously demonstrated that tamoxifen reduced risk of invasive breast cancer by 49% among women at high risk. Following this result, the US Food and Drug Administration (FDA) approved tamoxifen for breast cancer chemoprevention in women aged 35 years or more, with a 5-year breast cancer risk of 1.67% or higher.

In the current study, researchers at the National Cancer Institute (NCI), Bethesda, conducted a risk-benefit analysis using data from the US National Health Interview Survey Cancer Control Module, 2000. According to FDA

criteria, more than 10 million women aged between 35 and 79 would be eligible for tamoxifen chemoprevention. "A much smaller percentage would have an estimated net benefit," the researchers said.

Race was important. Almost 19% of white women would be eligible, compared with 5.7% of black women and 2.9% of Hispanic women. Among eligible white women, 4.9% would benefit, compared with 0.6% black women. This is because the overall risk for breast cancer is lower among black women, and rates of stroke, deep vein thrombosis and pulmonary embolism are higher.

Younger women were less likely than older women to experience the drug's adverse effects, but the highest percentage of women likely to benefit overall were aged between 40 and 59. Among the 2.4 million white women

likely to benefit from taking tamoxifen, 58,148 breast cancers would develop over the next 5 years. With tamoxifen, 28,492 cases could be prevented or deferred.

The study helps evaluate the potential public health impact of tamoxifen, but lead researcher Dr Andrew Freedman said the decision to take the drug is an individual one. "Women with increased risk of breast cancer must carefully consider the benefits and risk in consultation with their physicians."

Co-investigator Dr Worta McCaskill-Stevens agreed that the decision will depend on how a woman weighs the benefits and risks, her specific medical situation, lifestyle, personal values and preferences. "Tamoxifen therapy may not be appropriate for all women who are at increased risk for breast cancer," she said.

The menopause in cancer survivors

Premenopausal women who are about to begin chemotherapy or tamoxifen should be counselled about the possible precipitation of menopausal symptoms, researchers say (*Cancer Treatment Reviews* 2002, **28**, 321–333). "The consequences of premature menopause are of great importance to cancer survivors," according to the joint UK/Canadian group.

The rapid menopause associated with cancer treatment does not allow a woman's body to gradually adjust to falling oestrogen levels and hot flashes, for example, tend to be of a "more profound nature." Hormone replacement therapy (HRT) may be appropriate for symptom control in patients with tumours are not hormone dependent, but "patients with hormone dependent tumours will require safe and effective alternative treatments."

It is particularly important for breast cancer survivors, but the authors say that HRT "at the lowest dose possible" may be appropriate "in a small group of these women who have severe uncontrolled menopausal symptoms provided that they have a favourable prognosis, have remained free of recurrence for extended peri-

ods and are aware of the major limitations in the data available." However, national guidelines recommend that "Clinicians should remain cautious about using oestrogen replacement therapy in women with a previous diagnosis of breast cancer and particularly so in those with oestrogen receptor positive disease."

A structured, usually nurse-led approach, involving a tailored assessment intervention programme, has been shown to be effective in reducing symptoms. Other approaches considered in the review include use of tibolone, serotonin reuptake inhibitors, clonidine, phytoestrogens and vitamin E.

Cancer survivors should not be denied conventional cardiovascular prevention strategies, including the management of known risk factors such as hypertension, diabetes, and elevated lipid levels and the encouragement of smoking cessation. Risk of osteoporosis, another consequence of the menopause, should be reduced by smoking cessation advice, along with weight bearing exercise, treatment of metabolic or endocrine disorders and an adequate intake of calcium and vitamin D.

The pill and cervical cancer

Long-term use of the contraceptive pill may double women's risk of cervical cancer, researchers say (*Lancet* 2003, **361**, 1159–67). However, the public health indications of the findings "cannot be evaluated properly from established data", they say, since they depend on the extent to which the observed associations remain after use of the Pill has ceased.

Researchers from International Agency for Research on Cancer (IARC, Lyon, France), Cancer Research UK, Institute of Cancer Research, Sutton, and London School of Hygiene and Tropical Medicine, conducted a systematic review of 28 studies, including a total of 12 531 women with cervical cancer.

Relative risk increased with increasing duration of Pill use, and the effect remained when other risk factors for the disease, such as infection with human papillomavirus (HPV), smoking, or number of sexual partners, were taken into account. Women who had taken the Pill for 10 or more years had a relative risk of 2.2, compared with never-users. For HPV-positive women, the relative risk was 2.5.

PODIUM

Controlled use of off-label drugs

Professor Siegfried Seeber is Director of the Department of Medical Oncology and Haematology at the West German Cancer Centre, University of Essen, Germany. He is the current President of the German Society for Haematology and Oncology.



Professor Siegfried Seeber

How free are doctors in Germany to prescribe the drugs of their choice?

Our prescribing is checked retrospectively by doctors working for health insurance companies. As long as we prescribe according to the approved indications, costs must be reimbursed, no matter how expensive the drug is.

That sounds good — what's the problem?

There has been no increase in the general health budget since 2000, which means that the drugs budget has effectively been cut because salaries and other costs have risen. New drugs are far more expensive than older drugs, and, overall, drugs cost 8–10% more than before. Further, we have thousands of patients receiving drugs outside of official indications. That's because drugs companies often only register a drug for a single indication, knowing that when early results are presented at ASCO, clinicians will try the drug in other diseases. A drug might be registered for breast cancer because of good data from pivotal trials, although it is equally useful in

lymphoma. Quite often this happens by chance. Gemcitabine was registered for use in pancreatic disease, only later for lung cancer, and not yet for breast cancer. Good drugs are often good for many diseases but registered for only a few.

Almost 70% of our outpatient breast cancer patients are on off-label drugs such as gemcitabine, and most survive many years and much longer than 'median survivals' in prospective studies.

Why is recognition of off-label use so important?

Because it leaves clinical decisions in the hands of insurance companies. When a patient needs a drug which is not registered for their disease — this also applies to rare cancers where no drugs are registered — doctors have to write to their local insurance company office to ask permission to prescribe, and the insurance companies decide.

Offices in Berlin and Munich may give different answers to the same problem.

How widely recognised is the problem?

As President of the German Society for Haematology and Oncology, I issued a statement saying that controlled use of oncology drugs off-label must be allowed. As a scientific society, our position is that all drugs with a decent response rate must be allowed for individual patients, as long as they are responding.

Is the situation being addressed?

A Commission, including politicians, insurance company representatives and specialist doctors, is looking at the controlled use of off-label drugs. It's not just in cancer, but also in other fields like rheumatology where there are interesting but expensive new drugs. We'd expect a cancer drug to have done well in phase II trials, and shown a good response rate as 3rd or 4th line therapy, with acceptable time to progression. There won't be survival data because survival in most patients is determined by the total of all drugs taken, previously and afterwards. The drugs should only be used for as long as

patients are responding and stopped as soon as they become ineffective.

What is the outlook for the future?

Better therapies are more expensive and, because they're turning metastatic diseases into chronic conditions, they will be needed for longer. Treatment is going to become more expensive. If society is not able to pay for it, everyone should know this. It should not be the doctor's responsibility.

Does this put doctors under pressure?

Of course, and there is another serious development. In some cases, doctors' incomes are assessed within hospital budgets. If the hospital has overspent through use of expensive drugs, doctors may be punished indirectly. We do not think this is legal, but some doctors, such as those responsible for the budget for cytotoxic agents, may be under pressure to use older drugs in order to protect their own salary.

Why are budgets being introduced now?

3 or 4 years ago we could meet the costs of expensive new drugs. But now, in our field, there is an explosion of new drugs, each 6 to 8 times more expensive than the one they replace.

What is the public response in Germany?

The population contribute 13 to 14% of their salary on health insurance and expects to have everything. The Government and insurance companies are trying to restrict costs, for example by introducing new rules about follow-up after surgery. They want to exclude analysis of tumour markers and sonography, even though individual patients might benefit. It is becoming more restrictive.

What is the solution?

There is no good way out. Politicians think that patients need to contribute to costs. Another solution would be to restrict re-imbursement to really proven methods of diagnosis and treatment. It's a matter for debate at present.