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Alcohol, breast and colorectal cancer

Breast and colorectal cancers have been added to the list of cancers caused by alcohol, according to a forthcoming International Agency for Research on Cancer (IARC) Monograph (http://monographs.iarc.fr/ *and see volume* 96).

Pooled analysis of 53 studies on more than 58,000 women with breast cancer showed that daily consumption of 50g of alcohol is associated with a relative risk of about 1.5, compared with non-drinkers. Even consumption of 18g per day is associated with a small but significant increase in risk.

In colorectal cancer, pooled results from 8 cohort studies and meta-analyses found a relative risk of about 1.4 for colorectal cancer, with regular daily consumption of 50g.

These increases are smaller than the 2- to 3-fold increases in cancers of the mouth, pharynx, larynx and oesophagus, seen with a similar level of alcohol consumption. However, they are causing concern because breast and colorectal cancers are two of the most common worldwide.

'The clear association with increased risk of breast cancer associated with even modest levels of alcohol drinking is a major concern particularly in view of the changing drinking patterns of women in many countries. Public health action against alcohol consumption, especially excessive alcohol consumption, needs to be stepped up,' said Dr Peter Boyle, director of IARC.

Orphan status for enzastaurin

The European Medicines Agency (EMEA) has granted enzastaurin orphan drug designation for the treatment of diffuse large B-cell lymphoma (DLBCL). Although rare, DLBCL is the most common sub-type of non-Hodgkin's lymphoma (NHL) and approximately 50% of high-risk patients relapse within 3 years of receiving first-line therapy.

A phase III clinical trial, PRELUDE (Preventing Relapse in Lymphoma Using Daily Enzastaurin) is underway and is expected to enrol 459 patients across 100 sites worldwide. It is a randomised, placebo controlled study among DLBCL patients at high risk for relapse who have achieved remission following first-line therapy. Enzastaurin is being investigated as a maintenance therapy to prevent disease relapse and the primary endpoint will be overall disease-free survival.

Dr Richard Gaynor (Eli Lilly & Co) said, "In recent years, there has been progress in improving first-line therapies that help more patients achieve remission. However, our objective with enzastaurin is to develop an agent that may fill this important therapeutic need – the ability to keep DLBCL patients in remission."

Enzastaurin is an oral, serine threonine kinase inhibitor which selectively targets the PKCβ and PI3/AKT signalling pathways. These pathways are over-expressed in a variety of cancers and by blocking them, enzastaurin may suppress tumour cell proliferation, induce tumour cell death and inhibit tumour-induced angiogenesis.

Eli Lilly says that treatment has been well-tolerated with minimal drug-related toxicity. The agent is being studied in other tumour types including breast, colon, lung, ovarian and prostate cancers.

Annual breast MRIs for those at high risk

The American Cancer Society (ACS) has recommended annual magnetic resonance imaging (MRI) scans along with the standard yearly mammogram for women at high risk of breast cancer. Most should start this from age 30, the guidelines state (*CA: A Cancer Journal for Clinicians 2007;* **57**:75–89).

High risk women are defined as those with criteria such as:

- a *BRCA1* or *BRCA2* mutation,
- a first-degree relative with a *BRCA1* or *BRCA2* mutation, even if they have yet to be tested themselves,
- a lifetime risk of breast cancer scored at 20–25% or greater,
- they received radiation to the chest between the ages of 10 and 30.

Screening MRIs are not recommended for women with a lifetime risk of breast cancer below 15%, and the ACS guidelines state that, for those in between, with a 15–20% lifetime risk, there is not enough evidence to make a recommendation for or against MRI screening.

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doi:10.1016/j.ejca.2007.04.012

Inequalities in access to renal cancer drugs

New guidelines, issued by the European Association of Urology (Berlin, Germany, 21–24 March, 2007), place multi-targeted tyrosine kinase inhibitors (TKIs) at the forefront of treatment for metastatic renal cell carcinoma (mRCC). Patients across Europe, however, are being denied equal access to innovative therapies, resulting in a two tier system of treatment.

The "Guidelines on Renal Cell Carcinoma", based on a systematic Medline literature search and the Cochrane Central Register of Controlled trials, state that TKIs should be considered as first or second-line treatment for mRCC patients. Sunitinib malate (Sutent) is advised as first-line therapy in good- and intermediate-risk patients; while sorafenib (Nexavar) is advised as a second-line treatment for mRCC. In addition, temsirolimus (a specific inhibitor of mTOR), say the guidelines, should be considered as first-line treatment in poor risk patients.

Sunitinib received its full EU, marketing authorisation in July 2006 and approval for first line treatment in patients with advanced and/or metastatic renal cell carcinoma (mRCC) in January 2007. Authorization was based on a phase III study by Robert Motzer (*N Engl J Med 2007;* **356**:115–24) in which 750 patients with previously untreated mRCC were randomised to receive sunitinib or interferon alpha. Results show median progression-free survival was significantly longer in the sunitinib group (11 months) compared to the interferon alfa group (5 months).

Sorafenib received its EU licence in July 2006. In the phase III study, Bernard Escudier and colleagues (*N Engl J Med 2007;* **356**:125–34) randomised 903 patients with advanced RCC, who had progressed on or after first line therapy. They received oral sorafenib or placebo. Median progression free survival was 5.5 months in the sorafenib group versus 2.8 months in the placebo group. A further phase II study, also by Escudier, compared first line sorafenib with interferon alpha in 189 patients with unresectable and/or mRCC, and proved negative. The study presented at the 5th International Symposium on Targeted Anticancer Therapies (Amsterdam, The Netherlands, 8–10 March, 2007) found that progression free survival was comparable in both groups – 5.7 months for sorafenib versus 5.6 months for interferon. "This negative trial explains why sorafenib has not received a first line indication," said Dr Christian Doehn, (University of Lubeck Medical School, Germany).

It is unlikely that we will ever know whether either sunitinib or sorafenib make a difference to overall survival, he said, since trials allowed cross-over to the investigational drug after failure in the other arm. "Much work is still needed to understand the optimal application of these agents. The next step is to try sequence therapy and combination therapy of the different agents," said Dr Doehn.

While work continues to answer such questions, inequalities in access to TKIs are appearing across Europe. In France, Switzerland, Austria and Germany, access to drugs for the approved indication is unrestricted; once EMEA approval has been granted the patient's health insurance system pays automatically. In Sweden and the UK, however, all drugs are subjected to further economic evaluations before being funded.

'NICE PRODUCES SLOW, VARIABLE AND SECRETIVE ASSESSMENTS'

Sweden's Medical Products Agency (MPA) has already approved both sorafenib and sunitinib, but the UK's National Institute for Health and Clinical Effectiveness (NICE) has proved altogether tardier. NICE considered whether to schedule sorafenib for evaluation at a scoping meeting in February 2007, but has yet to announce its decision and has no plans to consider sunitinib. Since the Scottish Medical Consortium (SMC) turned down sunitinib for the treatment of second line mRCC on cost effectiveness grounds in January 2007, there are concerns that NICE will – eventually – follow suit. The SMC is currently receiving submissions for the review of sunitinib in first line treatment of mRCC.

"The MPA offers much more timely reviews than NICE and sets the threshold for allowing drugs through at €65,000 per quality adjusted life year gained, compared to a threshold of £30,000 (€45000) for NICE," says Professor Tim Eisen (University of Cambridge, UK). Furthermore, he adds, no standard economic assessment tools have been adopted by NICE, with each drug being sent out to different academics, using different tools, for assessment.

"Many clinicians accept the need for timely, fair and open cost-effectiveness assessment of health interventions. The problem is that NICE produces slow, variable and secretive assessments, with the result that UK patients have the worst access in Western Europe to cancer drugs," said Professor Eisen.

To obtain the drugs, UK oncologists have to apply to primary care trusts on an individual patient basis "Often the clinician and the primary care trust enter into long e-mail discussions which can drag on for 10 weeks before a final decision is reached. This causes unbearable uncertainty for patients who've no idea whether they will be awarded funding," says Professor Eisen.

John Wag staff (South West Wales Cancer Institute, Swansea, Wales), has 6 patients who have been denied treatment. "The general consensus amongst renal oncologists is that these agents represent the first advance in the management of this disease for 20 years. It's extremely frustrating that our patients cannot get access to them."

In the UK, the Commons Health Select Committee announced in February, 2007, that it is to conduct an inquiry into NICE. MPs will focus on why NICE's decisions have increasingly been challenged, and consider if public confidence has been damaged. They will also examine NICE's evaluation process, and whether it potentially disadvantages any particular groups. The committee will also look at how quickly NICE publishes its guidance - and whether it is implemented.

Janet Fricker

Janet Fricker was sponsored by Pfizer to attend the European Association of Urology Meeting in Berlin.

EUROFILE

Open access publishing in the EU

Open access publishing, long the subject of intense debate in publishing circles, is now attracting the attention of scientists and politicians. As of 21 March 2007, 24,000 scientists had signed a petition calling on the European Commission (EC) to mandate the publication of papers resulting from EU funding in open access archives, not later than 6 months after their appearance in journals.

The petition was launched on 18 January 2007, and organised by a variety of European research organisations including the Scholarly Publishing and Academic Resources Coalition (SPARC Europe), the German Research Foundation (DFG), the Danish Electronic Research Library (DEFF), the UK Joint Information Systems Committee (JISC), and the Netherlands higher education and research partnering organisation for network services and ICT (SURF). It follows the release of statements supporting open access by the European Research Advisory Board (EURAB), which advises the Commission on research matters, and the newly formed European Research Council (ERC).

In January 2006, the Commission published its study on the Economic and Technical Evolution of the Scientific Publication. "With the backing of organisations across Europe, this petition demonstrates the level of support for rapid and open access to publicly funded research,' said the organisers in a press release. The report resulted from a detailed analysis of the current scholarly journal publication market, together with extensive consultation with all the major stakeholders within the research communication process. It noted that 'dissemination and access to research results is a pillar in the development of the European Research Area.'

A year after publication of the study, the petition organisers urged the EC to endorse the recommendations in full. 'Research must be widely disseminated and read to be useful,' the petition suggests, going on to outline the economic advantages of widening access to publicly funded research, including the encouragement of further research and promotion of European research outputs worldwide.

At a conference on scientific publishing in February, 2007, Research Commissioner Janez Potočnik, indicated that the Commission would not be slow in taking this up. "Nearly all new research builds on previous work", he said. "So access to scientific results, how rapidly this access is given, and the cost of access all impact on research excellence and innovation."

In a discussion paper timed to coincide with the conference, the Commission confirmed that it will promote better access to publications resulting from the research it funds in future.

'RESEARCH MUST BE WIDELY DISSEMINATED TO BE USEFUL'

Open access publishing projects will be eligible for EU funding, and €50m will be used to link digital repositories over the next two years. Later in 2007, the commission will set up a study into the economic aspects of digital repositories. It has also announced that when it reviews value added tax (VAT), it will consider the impact of the tax on scientific publications.

As publications move from print to digital, the Commission will "encourage experiments with new models that may improve access to and dissemination of scientific information."

Many funding agencies are already requiring researchers to make their published papers freely accessible. On 1 October 2006, the UK's Wellcome Trust and Medical Research Council began requiring grantees to deposit final, peer-reviewed manuscripts in public databases as soon as possible, but no later than 6 months of publication. Failure to do so, said Mark Walport, Wellcome Trust director, would breach the conditions under which grants were awarded.

In January, 2007, Cancer Research UK joined with a number of other leading British research funders to create the UK PubMed Central Repository. "All our research is paid for by the public so we feel it is our duty to make sure people can see what their money is spent on. Access to our work for both the public and researchers is incredibly important to us", said Julia Chester, Director of Knowledge Management at CRUK.

The repository puts published papers on-line after their appearance in a traditional journal. "Some publishers allow us to do this earlier than others", said Chester. "Overall the average is 6 months. Although we would like to put papers in the repository as quickly as we can, we appreciate that it is a difficult situation for scientific societies who only publish one journal".

Furthermore, the European Institute of Oncology has announced plans to launch an open access journal – ecancerscience.com – in the autumn of 2007. "We'll be able to turn papers round in 3 weeks by using only one peer-reviewer," said Professor Gordon McVie, who is leading the venture with Professor Umberto Veronesi. "Further peer review will come in the form of on-line comment, thereby giving other scientists the chance to give their views on new research immediately."

Debate about the principle of open access publishing is ongoing, though, and barriers may need to be overcome for it to flourish. A recent US/German study (http://openaccess-study.com/) found an extremely positive attitude towards open access among 688 publishing scientists. "However, many seem to be rather reluctant to publish their own research work in Open Access outlets," the study found.

Advantages of speed and reach "are seen alongside insufficient impact factors, lacking long-term availability and inferior ability to reach the specific target audience of scientists within one's own discipline", the study concluded.

Mary Rice
Brussels

Is it all over for erythropoietin?

A spate of recent reports has increased suspicions that the use of erythropoietin to prevent or treat anaemia in patients with cancer might reduce their survival.

Anaemia is a common complication in patients with cancer, particularly in those undergoing radio- or chemotherapy. However, by stimulating the division of erythrocyte precursors, erythropoietin, one of the world's most commonly used cancer-care drugs, reduces the need for transfusions. In addition to theoretical improvements in patients' quality of life, some reports even suggest this treatment renders tumours more radio-and chemosensitive. Yet increasing evidence suggests that erythropoietin might stimulate the growth of tumours and reduce patient survival.

Recently, four trials of different erythropoietin drugs used at different doses to treat anaemia in patients with different types of cancer, either receiving or not receiving treatment for their disease, have been reported as halted due to associations between use of the drug and worsening locoregional disease or reduced survival (see *J Clin Oncol* published online Feb 20, 2007; DOI:10.1200/JCO.2006.07.1514 and margin). While these trials are quite different in terms of their patients, design, and endpoints, the cessation of erythropoietin treatment in these studies has caused considerable unease.

'QUESTIONS REMAIN ABOUT THE SAFE DOSE AND HAEMOGLOBIN TARGETS'

Author of the 2007 *J Clin Oncol* article, James Wright (Juravinski Cancer Centre at Hamilton Health Sciences, Hamilton, Ontario, Canada) comments: "Concerns about survival and locoregional control of disease in patients treated with erythropoietin came to the fore in 2003. when two studies (*J Clin Oncol* 2005; **23:**5960–72, *Lancet* 2003; **362:**1255–60) on preventing anaemia in patients with metastatic breast cancer and with advanced head and neck cancer suggested the drug was achieving the opposite to that expected of it. Survival was worse among patients with breast cancer and the drug actually seemed to encourage tumour growth in patients with head and neck cancer rather than help prevent it. Although later analysis showed these trials had problems making it difficult to tell whether these effects were real, there remained concerns that the drug might be stimulating tumour cells, possibly through erythropoietin receptors on the cell surface, thus encouraging, rather than preventing their growth. Although meta-analyses (*JNCI* 2005; **97:**489–98 and *JNCI* 2006; **98:**708–14) performed after our trial ended have found it difficult to determine a definitive effect on survival, they have reported that erythropoietin may increase the risk of thromboembolic events and suggest caution in its use in patients with cancer".

The results of these different trials are hard to compare, but they undoubtedly raise questions about what the safe dose of erythropoietin might be, the targets for haemoglobin concentrations, and which (if any) patients might benefit from this treatment.

"I think erythropoietin still has an important role in sparing anaemic patients with cancer from red cell transfusions", says David Steensma (Mayo Clinic, Rochester, NY, USA). "However, the recent studies suggest that bringing haemoglobin all the way up to normal [110–120 g/L] or supranormal levels may be problematic. Additionally, erythropoietin may have more limited benefits in patients with cancer who are not actively receiving anti-neoplastic treatment."

'TRIALS ONLY MAKE SENSE IN A FEW SELECT POPULATIONS'

Jerry Spivak at the Johns Hopkins University, Boston, MA, USA, agrees. "I do not believe that there is sufficient evidence to suspend the use of recombinant erythropoietins in anaemic cancer patients perse. There is, however, sufficient evidence to suspend their use in anaemic patients with nonmyeloid malignancies who are not receiving chemotherapy, and to limit the target haemoglobin to 110 g/L in those who are receiving chemotherapy."

Wright continues: "[As long as] consent can communicate appropriately the uncertainty of a survival effect in the specific population under study, then trials would be OK to continue, but they would probably only make sense in a few select populations while sticking close to the approved indications, ie, chemo-induced anaemia (not disease- related), and not for quality of life as the primary outcome".

Steensma adds the caveat: "I would have a problem now enrolling a patient with cancer on a study that used erythropoietin to try to prevent anaemia rather than treat it, or a study that targeted haemoglobin of >130 g/L".

'I WOULD NOT USE ERYTHROPOIETIN TO PREVENT ANAEMIA'

"Given the [reduced survival of] the anaemic patients with advanced non-small-cell lung cancer in [the article by Wright et al], and the lack of a transfusion benefit, it makes little sense to employ an erythropoietic stimulating agent in this type of setting or even to proceed with further clinical trials in this clinical situation", comments Spivak.

Unfortunately, patients are now affected by the confusion about the use of erythropoietin for the prevention and treatment of anaemia. Hopefully, the US Food and Drug Administration's Oncological Drugs Advisory Committee which meets to discuss the drug on May 10, 2007, will make firm suggestions regarding where to go from here.

Adrian Burton

For more information on the three other halted studies see *http://conman.au.dk/dahanca, http://www.amgen.com/media/media_pr_detail.jsp?releaseID=954402, and http://www.roche.com/med-cor-2007-02-23c*

This story originally appeared in Lancet Oncol 2007 **8:**285.

PODIUM

Why Finland is top of the Euro cancer league

Pirkko-Liisa Kellokumpu-Lehtinen is professor of radiotherapy and oncology at Tampere University Hospital, Finland. She gave a talk entitled 'Why Finland is top of the Euro Cancer League' at a European School of Oncology conference in Brussels, Belgium, in November 2006.

In what sense is Finland top? Do you mean in survival?

We have good survival rates because we have good prevention programmes, strong anti-smoking laws, and nationwide screening programmes which are free-of-charge. Screening for cervical cancer has been ongoing since the mid 1960s; screening for breast cancer (mammograms every second year) was introduced in the mid 1980s. We have on-going studies of screening in prostate and in colorectal cancer.

Treatment in Finland is centralised and most is given at university hospitals where national guidelines are followed. Our follow up of late side effects is not as good as it could be, though.

The national cancer registry has been running for 50 years, and the Cancer Society of Finland, which runs patient groups, counselling, and so on, for 70 years.

So Finland's success is down to the organisation of cancer services?

The education and quality of our doctors is also important. Most oncologists spend 3 to 4 years training in a university hospital and are assessed by a specialist examiner. This system has been in place for 40 years.

We are involved in national and international research into better treatment modalities. The FinHer study (*NEJM 2006;* **354**:809–820) found that, among women with *HER2/neu*-positive breast cancer who were receiving either docetaxel or vinorelbine, the addition of only 9 weeks of trastuzumab was associated with an improved 3-year recurrence-free survival.

Does the system work because Finland is a small country?

We have always had a far-sighted national policy, based on the idea that it is more expensive to treat than to prevent or detect early. Our health education and social system is good. The healthcare system is covered by taxes and the whole family uses it.

It's been said that Finland has a remarkably obedient population?

They are well-educated about health and understand what we are trying to achieve. When a new type of polio vaccine was introduced some years ago, a nationwide vaccination programme was organised and more than 90% of the population attended over a single weekend. Similarly, in clinical trials, patients attend when they're invited, and keep coming through the follow-up.

Could aspects of the Finnish system be used in other countries?

Every country would benefit from education at every level. Health messages need to be conveyed to mothers of babies, children at primary and secondary schools, university students, young people joining the army for national service, and so on. Education should not be just isolated invitations to screening, but a long term programme aimed at young and old alike.

Is this an expensive approach?

Actually, Finland spends less than the average in Europe, and less than other Nordic countries. Salaries for nurses are quite low here, but this is not the only reason.

Is Finland set to stay at the top of the league?

Other countries are catching up. Our 5 year survival for breast cancer is 88% and it is difficult to improve beyond that. We detect breast cancers early, which is one reason for the good survival rates, but the other is our use of adjuvant treatment. In lung cancer, although rates among men are going down, women are smoking more and lung cancer is increasing among women here. In general, the population is fatter and takes less exercise.

What is the Finnish approach to expensive new drugs?

It is hard. We use drugs with a good evidence-base, such as Herceptin. But there are always negotiations within hospitals about expensive drugs. Using MabThera in lymphoma, you can cure up to 20% patients, so the drug is not expensive when you consider quality-adjusted life-years. But it is almost impossible to use expensive drugs which extend life only slightly.

We have national guidelines for common cancer types: prostate, lung, ovarian and so on. Otherwise, decisions come down to individual hospitals or oncologists. Evidence-based care is carefully budgeted for and planned. A national body, Finofta evaluates some treatments but we have no system like the UK's NICE (National Institute for Health and Clinical Excellence); we're discussing whether we should have.

What challenges lie ahead?

Over the next 10 years, we are expecting to have 25–30% more new cancer patients as the post-war baby boom is reaching the age when cancer is common. We need to keep sufficient numbers of nurses and doctors in the field of cancer, and find the money to apply good results. Where new molecules acting on specific cancer types have been shown to improve cure rates, it is a huge task to pay for them. Funding nationwide colorectal screening is another challenge but screening is part of the Finnish philosophy and we are ahead of other countries in this.