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European Journal of Cancer 39 (2003) 1811–1815

European Journal of Cancer

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ASCO's 39th Annual Meeting (May 31–June 3, 2003) took place in Chicago, Illinois. Emma Cannell, *EJC* Scientific Editor, reports here on pages 1811, 1812 and 1814

Biology not chronology should determine treatment

Older women with node-positive breast cancer respond as well as younger women to adjuvant chemotherapy, according to Dr Hyman B. Muss (Univ. of Vermont, Burlington, VT). Reporting on behalf of the Cancer and Leukemia Group (CALGB) at the 39th Annual meeting of the American Society of Clinical Oncology (ASCO), he said, "Using age alone is a bias".

Dr Muss presented data on 6489 patients in 4 CALGB trials from 1975 to 1999 examining the benefit and toxicity from adjuvant chemotherapy treatment after surgery. It showed that similar dose-related benefits in reducing breast cancer-related relapse and mortality were observed for women aged 65 years and over compared with those under 50. (*Proc Am Soc Clin Oncol* 2003, **22**, 4).

Risk of breast cancer increases with age, but older women are often not offered treatment due to misconceptions that they may have more indolent disease and will benefit less because of competing comorbidities. Although around 50% of patients in the US are aged 65 years and older, only 542 (8%) of these patients were included in the CALGB studies and the older patients who were selected tended to have more involved lymph nodes than the younger women.

Dr Hyman B. Muss. Photo courtesy © ASCO/Todd Buchanan 2003

The older group—as might be expected—had a slightly higher treatment-related mortality (7/542 compared with 8/3506 for those aged < 50 years) and a higher overall mortality due to deaths that were unrelated to breast cancer.

Dr Muss said, "The job of physicians is to give the best treatment to patients and using age alone is a bias. . . .We want to do the right thing for our patients."

Other studies at ASCO reported that older cancer patients are underrepresented in treatment groups (*Proc Am Soc Clin Oncol* 2003, **22**, 728); and those with advanced disease are less likely to be referred to oncologists (*Proc Am Soc Clin Oncol* 2003, **22**, 761). Dr G. Curigliano (European Institute of Oncology, Department of Medicine, Milan, Italy) found that only 6.4% of women with breast cancer aged > 75 years were offered chemotherapy compared with 35.4% of women aged between 50 and 75 years (*Proc Am Soc Clin Oncol* 2003, **22**, 762). "We should consider the biological age and not the chronological age of the patients", he said.

'First real advance' in spinal cord compression

Patients treated with surgery and radiation for spinal cord compression are more likely to remain ambulatory and continent than those treated with radiation alone, according to a study conducted at the University of Kentucky (*Proc Am Soc Clin Oncol* 2003, **22**, 1). "Patients treated with surgery and radiation were able to walk essentially as long as they lived", said Dr Roy Patchell, the lead investigator of the study.

The investigators randomised 101 patients with spinal cord compressions to either combined treatment or radiation alone (30 Gy for both groups). Those patients who underwent surgery were able to walk on average for 126 days compared with only 35 days for those given radiation alone. More than half (56%) of the surgical patients regained the ability to walk compared with 19% of those given radiation alone. There was a non-significant trend for better survival in the surgical group (median of 129 days compared with 100 days).

The protocol allowed 20% of the radiation patients to crossover to the surgical arm of the study. Although 30% of these patients regained the ability to walk, there was a high complication rate after salvage therapy (40% compared with 12% for those given surgery as their initial treatment). "Surgery and radiation is better and should be given as upfront treatment", he said. "This study is the first real advance in the treatment of this condition made in the last 30 years". The study was stopped early due to the differences observed between the 2 arms.

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0959-8049/$ - see front matter
doi:10.1016/S0959-8049(03)00606-3

ASCO
AMERICAN SOCIETY OF CLINICAL ONCOLOGY

MRI 'better than mammography'?

Magnetic resonance imaging (MRI) was more sensitive, but generally less specific, than mammography in women with a family history of cancer, 3 studies reported at ASCO. "MRI is the most powerful tool to detect cancer. . .. and avoid unnecessary biopsies" said Dr Christiane K. Kuhl (University of Bonn, Germany), the lead investigator of one of the studies.

Dr Kuhl reported 5-year screening results from 462 known or suspected gene carriers. (*Proc Am Soc Clin Oncol* 2003, **22**, 2). Women were examined yearly by a clinical breast exam (CBE), 2-view mammography, high-resolution ultrasound and MRI. In 45 women, 51 breast cancers were identified. MRI had a higher sensitivity (96.1%) than mammography (42.8%), ultrasound (47%) and CBE (25%). MRI was also more specific. (95.1% compared with 88.4% for ultrasound and 94.3% for mammography).

Women with a family history are often screened as early as 30 years of age when their breasts may be quite dense limiting the usefulness of mammograms. Furthermore, Dr Kuhl believes that these women could be harmed by the ionising radiation from mammograms as their inherited mutation(s) may make them more susceptible to its DNA damaging effects. Since screening starts early,

Dr Christiane K. Kuhl. Photo courtesy © ASCO/Todd Buchanan 2003

these women are likely to undergo many more mammograms than older women. "It may be better to replace mammography with MRI in women with a documented mutation", she said.

Reporting on the largest study to date, Dr Mieke Kriege (Erasmus University Medical Centre, Rotterdam, The Netherlands) was more cautious. His study identified 34 invasive cancers from the 1874 eligible women in the Dutch MRI Screening study. The relative sensitivity of MRI for invasive tumours was 83% compared with only 37% for mammography (*Proc Am Soc Clin Oncol* 2003, **22**, 2). However, the specificity was lower.

His results were mirrored in a study of 54 BRCA-positive women from the Memorial Sloan-Kettering Cancer Center (MSKCC), where MRI had 100% sensitivity, but was only 83% specific (*Proc Am Soc Clin Oncol* 2003, **22**, 91). Annual mammography identifies around 80% of cancers. "MRI can clearly detect breast abnormalities that are not seen by mammography. Unfortunately, we are finding that many of these abnormalities are not cancer", said Dr Mark E. Robson, the lead MSKCC investigator.

All of the investigators agreed that the value of MRI would increase as centres became more expert and specialised in its use. This should help reduce the false-positives and drive the costs down, as it is currently more expensive than mammography.

Cardiovascular drugs may reduce cancer risk

Statins, drugs that lower cholesterol levels, may reduce the risk of cancer, according to the results of a case-control study by Dutch researchers. " The impact on public health may be considerable," said Dr Matthijs Graaf (Academic Medical Centre, University of Amsterdam, Amsterdam, Netherlands), the lead investigator of the study.

Animal studies have suggested that statins—which are used in cardiovascular patients—have an anti-tumour potential. They work by inhibiting an enzyme involved in the ras signalling pathway, a pathway that is important in the development of cancer.

The investigators used data from pharmacy and hospital records in 8 Dutch cities to compare statin use in 3080 patients with cancer with 16 711 controls, matched for age, gender and calendar period.

Statin users had a 20% reduction in cancer risk (*Proc Am Soc Clin Oncol* 2003, **22**, 846). The effect was dependent on the duration of treatment and

Dr Matthijs Graaf. Photo courtesy © ASCO/Todd Buchanan 2003

the cumulative dose received. It was greater in those that had received more than 1350 daily doses (40% reduction) and those who had been treated for more than 4 years (36% reduction). Risk reductions were particularly noted for tumours of the prostate and kidney. Risk values returned to baseline levels 6 months after stopping statin treatment.

Although some confounding factors were controlled for, the study was limited by a lack of information on lifestyle factors such as smoking that may have biased the results. Nevertheless, the risk of lung-associated cancers did not differ between the 2 groups. "This is a case-control study and we need more evidence before we can encourage the general public to take them to reduce their risk", he said.

EUROFILE

Thumbs down for Clinical Trials Directive

Widespread dissatisfaction with the European Directive on clinical trials was expressed at a conference in Brussels, June 2003. Even the European Commission (EC), which initiated the directive in an attempt to strengthen clinical trials work, is unhappy with the final result, delegates heard.

The conference was organised by the European Forum for Good Clinical Practice and the European Cancer Research Managers Forum, and supported by the EC and the European Organisation for Research and Treatment of Cancer.

Research Commissioner Philippe Busquin said that the Directive was intended to simplify and harmonise clinical trials work across Europe. It was intended to "organise the strength of diversity into coherence", he said.

'EUROPE COULD BE TRANSFORMED INTO THE POOR RELATION'

Philippe Brunet, head of the pharmaceuticals unit in DG Enterprise, was more candid. In suggesting the Directive, the Commission was trying to overturn a tradition of weak trials and make them more enduring. It is unhappy with the final form of the Directive, which is very different to what was intended. It is a *fait accompli*, however, he warned, and there is no point in trying to overturn or amend it at present.

Delegates were equally unhappy with the regulations, which have to be transposed into national laws in all the EU Member States by May 2004. Dr Richard Sullivan (Cancer Research UK) said that academic trials are essential for the future of public health, but there has been little academic input into any European public health legislation.

The heart of the problem lies with the definition of a 'sponsor', as "an individual, company, institution or organisation, which takes responsibility for the initiation, management and/or financing of a clinical trial." This appears to be have been drafted with the pharmaceutical industry in mind. For collaborative academic research partnership, defining who the sponsor is seems to be well nigh impossible- and fraught with danger since the requirement will expose a single sponsor to the risk of litigation.

The definition of an "investigational product" as any product used in a clinical trial, and the requirement to supply all drugs free of charge, as well as to use special labelling, packaging, storage and handling, are also major issues for academia. Any drug administered in a trial will automatically be considered to be a research product, even if it has already been approved for the disease studied.

Academic researchers estimate that the new regulations will increase the cost of clinical trials by at least 30% and double the administrative burden for sponsors, with no evidence that trial quality of personal safety will be improved. "The end result will be that academic researchers will be unable to conduct independent evaluations of drugs, and the only clinical studies in existence will be those run by the pharmaceutical industry", said Dr Martine Piccart (Institut Jules Bordet, Brussels, Belgium), chair of the Breast International Group, a network of leading international specialists.

At the conference, people from all sides were equally pessimistic. "One of the key issues here is that academia is being asked to do things that industry has done for years, but within existing resources" said George Blackledge, Vice President, AstraZeneca. "These things cost money."

Representatives from several national authorities said that they have decided to take into account the necessity to provide some trial drugs for free, on the grounds of public health and the ability of institutions to pay for them. Delegates were urged to put pressure on their national authorities to make sure that this applies in all EU member countries.

Some national pharmaceutical associations have also been active in support of academic research. A statement from the Association of the British Pharmaceutical Industry said: "Despite the stated purpose of the Directive it is clear that the planned changes in the UK and the rest of Europe will not simplify, and are unlikely to result in substantial harmonisation of, the current regulatory procedures for the conduct of clinical trials. There are many new requirements which will place an administrative burden on both sponsors of clinical trials and on regulators."

Summing up, Octavi Quintana-Trias (Health Directorate, DG Research) said that if Europe wants to close the research gap with the US, money will have to be found to support academic trials. Society and decision-makers need to understand that, but there will be no money from the Commission for it. A new source of money will have to be found, but harmonisation means giving up national sovereignty and Member States do not like it. More trials should be submitted to the Commission as projects for funding, he said.

"We believe that European Union Member States are not fully aware of the negative consequences of this Directive, which could transform Europe into the poor relation of other countries that carry out independent clinical investigations" said Dr Piccart. "We cannot believe that this is what those who regulate clinical research really want."

But why did everyone miss out on the opportunity to influence matters at a much earlier stage? The pharmaceutical industry succeeded in getting a number of amendments to the Directive adopted. Of course, they have more resources, but they also have considerably less credibility with legislators than do medical academics. It's a shame that this credibility isn't always used at a time when it could have a real effect.

Mary Rice,
Brussels

Gene polymorphisms may predict neutropenia

Predicting which patients treated with irinotecan will experience toxicity is currently extremely difficult, but researchers reporting at ASCO have identified genetic alterations that may help. "We need more data, but this study lays the foundation", said Dr Mark Ratain (University of Chicago Medical Center, Chicago, IL).

The investigators treated 66 patients with irinotecan and all patients underwent *UGT1A1* genotyping. This gene is responsible for the conversion of the active metabolite of irinotecan (SN-38) into an inactive form. Any reduction in this conversion is expected to increase the toxicity experienced by the patient. The gene is highly polymorphic and exists in 2 forms- 6 and 7. The 7 form (referred to as *UGT1A1**28(TA_7)) has an extra TA repeat in the TATA sequence of the promoter and is thought to have a reduced ability to convert SN-38 to its more inactive form.

Grade 4 neutropenia was experienced by 5 of 61 patients; and 3 had the 7/7 genotype (*Proc Am Soc Clin Oncol* 2003, **22**, 124). No patients with the 6/6 genotype developed neutropenia. For those with the 7/7 genotype, the test has a 60% sensitivity, 94% specificity and 96% negative predictive value for predicting grade 4 neutropenia.

The researchers have also identified another polymorphism that from preliminary studies is even more predictive and they hope that with more research it will be possible to individualise the dosing of patients by predicting those who are at a low and high risk of toxicity. "The study's results underscore the need to identify patients genetically predisposed to severe side-effects from irinotecan treatment", he said.

Dr Mark Ratain. Photo courtesy © ASCO/Todd Buchanan 2003

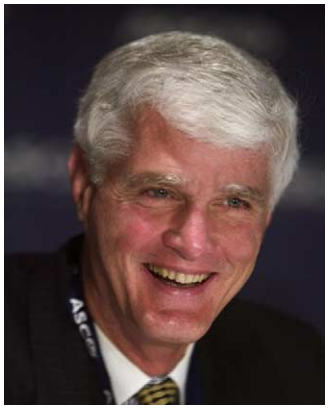
Tobacco: the "true weapon of mass destruction"

Tobacco control was one of the key themes of the 2003 ASCO meeting. "As an American, I am horrified we are exporting this substance of death around the world", said the ASCO President, Dr Paul A. Bunn, Jr (Director of the University of Colorado Cancer Center), speaking at the Plenary session of the meeting. He outlined ASCO's revised policy on tobacco (available on the society's web site http://www.asco.org).

ASCO's stated aim is a tobacco-free world and it has set up an independent blue-ribbon commission to study the social, medical, legal and economic aspects of the problem, both domestically and worldwide. It hopes that the broad-based membership will enable the commission to adopt a more comprehensive and less fragmented approach than in the past, and deliver a workable strategy. "We can no longer tolerate a lack of direction and a lack of progress", said Dr Bunn.

The statement acknowledges that this will take time, but outlines measures that can be implemented immediately. These include raising federal taxes, increasing efforts to reduce tobacco use in the young, restricting smoking in public places, supporting research into nicotine addiction and halting government promotion of tobacco products. "I hope our government will support our efforts to eliminate this 'true weapon of mass destruction'", he said.

ASCO has issued a statement in support of a report by the Interagency Committee on Smoking and Health that calls both for increases in federal taxes and the integration of smoking cessation into basic insurance coverage.



Dr Paul A. Bunn. Photo courtesy © ASCO/Todd Buchanan 2003

Stopping smoking works

Stopping smoking works and the earlier the better, said Professor Sir Richard Peto (Clinical Trials Service Unit, Oxford University, UK). "Half of all smokers are killed and a quarter will die in middle-age losing around 25 years of life", he said. Even stopping at 50 years old cuts the risk of dying from lung cancer by the age of 75 to around 6%, compared with 15% for those who continue.

In the UK, where there are approximately twice as many ex-smokers as smokers among those over 50, mortality from lung cancer is decreasing. In France, however, efforts to stop smoking have lagged behind and rates are still increasing. Nevertheless, cigarette prices in France recently doubled, indicating a willingness to tackle the problem.

Tobacco use is responsible for around one third of all cancer deaths. Reducing this number will require adult cessation as well as stopping young people from starting. "I am not telling people what to do, but just telling people what is known", Professor Peto said.

PODIUM

Weighing up the evidence

Dr Chris Williams is Director of the UK's Cochrane Cancer Network, which coordinates systematic reviews of evidence from randomised clinical trials. He is a member of EORTC's Protocol Review Committee and a former Chairman of the UK's Medical Research Council (MRC) Cancer Therapy Committee. He trained at London, UK, and Stanford, USA, and is based in Bristol, UK.

Dr Chris Williams

What is evidence-based oncology?
Oncology based on the best synthesis of the best evidence available, using methods designed to avoid bias.

Is it practised at present?
Not often. Most clinical decisions are based on prior experience, anecdotal evidence and information read recently. They do not take into account the generality of information and have no systematic way of avoiding bias.

Does the lack of evidence-based practice cause problems?
We don't know. A systematic review of the high-quality *Journal of Clinical Oncology*, for instance, found that less than 10% of its reviews use any systematic methods; 90% of its reviews are potentially biased. We don't know exactly what impact this has, though systematic reviews have shown that sometimes we are using treatments we should have known do not work, and the converse. For example, the use of ovarian ablation as an adjuvant therapy for breast cancer was rejected 20 years ago. A number of clinical trials each found no evidence that it was effective, but a systematic review with long term follow up of 14 years or more concluded that it clearly improved outcome.

Do systematic reviews mean the end of the narrative review?
No, but narratives should be based on systematic reviews, and interpret them for use in clinical practice and in deciding on the direction of new research. Interpretation can depend on cultural and economic factors. Current evidence suggests that chemotherapy for non-small cell lung cancer gives a modest survival benefit. It's quite plausible that in North America, this is interpreted to mean every patient should receive it; in Europe, that selected patients should receive it; and in Africa, that nobody should. The evidence is objective, but its interpretation might not be.

Does it apply to all areas of oncology?
There are areas where there is no good evidence, such as for the treatment of rare tumours, and others where, ethically it is impossible to conduct randomised controlled trials (RCTs). Having said that, you can still be systematic in collecting the best evidence even if the synthesis is much less authoritative.

What is the particular strength of the systematic review?
It depends on the quality of the original studies. Where there are plenty of prospective RCTs, a systematic review may well give a clear answer. But even where original RCTs are lacking, a systematic review should help improve the design of subsequent trials. The MRC in the UK insists that all grant applications for clinical trials include some sort of systematic review. If all grant-giving bodies did the same, it would be a step forward.

When researchers write up trials, I'd like to see them also conduct a systematic review of the literature, and update it to include their own work. It would require a certain honesty, as they would have to consider their own work alongside everyone else's, but it would be much more useful to readers.

How good is the literature?
People conducting their first systematic review are astonished by its poor quality. Even large studies do not always give enough information to be included in a systematic review. If a trial claims to be randomised, we need to be sure that the randomisation was done properly—not by month of birth, for example.

The large, pragmatic, multigroup trials are improving the overall quality. But we know that about 20% of trials are never reported; half the abstracts presented at meetings are never written up as a full paper. This creates an inbuilt bias in the literature because these studies are more likely than others to be negative.

What do you hope that the book, Evidence-based Oncology, will achieve?
The aim was, for the first time, to produce a cancer textbook that gathers all the evidence together and presents it in an unbiased way. It doesn't cover the whole of oncology, but rather picks out key questions and looks for good quality systematic reviews, or, where these do not exist, the best quality trials.

Evidence-based medicine has only been going 10 years. We've had clinical trials for 50 years and we still haven't got those right! It's going to take time for evidence-based oncology to become widespread in practice. It will require oncologists to be sophisticated in the way the read and appraise the literature.

'Evidence-based Oncology', edited by Dr Chris Williams, is published in the UK by BMJ Books, ISBN: 0 7279 1439 1. The Cochrane Cancer Network is at http://www.canet.org and the evidence-based oncology section of Cancer Treatment Reviews is at http://www.elsevierhealth/journals/ctrv