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31st Annual San Antonio Breast Cancer Symposium December 10–14, 2008

Breast density 'indicates tamoxifen efficacy'

Tamoxifen's likely efficacy in preventing breast cancer can be predicted from breast density changes, UK researchers said (#15).

In 2007, IBIS-1 showed that prophylactic tamoxifen reduced breast cancer risk by 40%, and also reduced breast density as seen on a mammogram. The current study focused on whether changes in breast density after 12–18 months of tamoxifen could predict breast cancer development.

Researchers reviewed mammograms taken at entry and at 12–18 months for 120 women in IBIS-1 who subsequently developed breast cancer. They were compared with 943 controls (who did not develop breast cancer).

A multivariate analysis of women in the tamoxifen arm (48 cases and 456 controls) found that only changes in mammographic density were significant predictors of risk. Furthermore, in the tamoxifen arm, where density was reduced by 10% or more, breast cancer risk was reduced by 63% compared to women whose breast density was reduced by less than 10%.

Principal investigator Jack Cuzick (London, UK) likened the use of breast density as an indicator of tamoxifen efficacy to the use of drugs and biomarkers in cardiology. 'Cardiologists don't wait for a patient to get a heart attack. They monitor blood pressure and cholesterol and make treatment decisions as needed,' he said.

An important remaining question, he added, is whether the breast density effect is only for tamoxifen, or could be used to predict the efficacy of other preventive strategies, such as raloxifene (Evista).

Zoledronic acid 'shrinks tumours'

Zoledronic acid (Zometa) plus standard chemotherapy reduces the size of breast tumours before surgery more effectively than chemotherapy alone in early disease, researchers say (# 5101).

In the phase III AZURE study, researchers carried out a retrospective pathology analysis on a subgroup of 205 pre- and post-menopausal women receiving neoadjuvant chemotherapy.

Patients in the zoledronic acid arm had a median residual tumour size of 20.5 mm compared with 30 mm among those receiving chemotherapy alone. Fewer patients in the combination arm required mastectomy.

Researchers stressed that the study was hypothesis-generating rather than practice-changing as the finding needs to be studied in more detail.

The anticancer properties of zoledronic acid were first presented at ASCO 2008, by Michael Gnant (University of Vienna, Austria). The ABCSG trial found that addition of zoledronic acid to endocrine therapy reduced the risk of recurrence by 35% compared to endocrine therapy alone.

BIG data on letrozole

The aromatase inhibitor letrozole may confer a benefit in overall survival in the adjuvant setting, compared to tamoxifen (#13).

New data from the Breast International Group (BIG) 1–98 study of postmenopausal women with hormone receptor positive early-stage breast cancer was presented. At a median of 76 months, patients taking letrozole had a 13% reduction in risk of death, compared to those on tamoxifen.

Test for chromosome 17

Women with a duplication of chromosome 17 in their breast tumour will benefit from anthracycline drugs; others can be spared the side-effects of treatment, Cancer Research UK scientists said (#45).

The research team examined samples from 2,500 women to identify which markers could predict whether the chemotherapy treatment would be successful.

The test is already available. Lead author professor John Bartlett (Edinburgh, UK) said, 'We are now close to being able to use this new marker in the clinic to select appropriate therapies in early breast cancer.'

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Uric acid control

Data from a phase III study, led by Jorge Cortes (Houston, TX, USA), suggest that rasburicase produces better and faster control of serum uric acid than allopurinol in patients with haematological malignancies at risk from tumour lysis syndrome. The investigators compared rasburicase (0.20 mg/kg per day, days 1–5, n = 92), with allopurinol (300 mg/day, days 1–5, n = 91). Rasburicase, a recombinant urate oxidase, reduces serum uric acid through conversion of uric acid to allantonin. Results show that concentrations of serum uric acid normalised by days 3–7; normalisation was achieved in a greater proportion of patients who received rasburicase than of those who received allopurinol (p = 0-0009). Time to serum uric acid control was 4.1 h in the rasburicase group versus 27 h in the allopurinol group. No differences in the incidence or severity of adverse events were reported.

Thromboembolism

Nadroparin reduces the incidence of thromboembolic events in patients with cancer receiving chemotherapy, concludes the PROTECHT study. Giancarlo Agnelli (Perugia, Italy) and colleagues randomly assigned 1166 patients with metastatic or locally advanced lung, breast, gastrointestinal, ovarian, or head and neck cancers 2:1 to receive either subcutaneous injections of nadroparin (3800 anti-Xa IU once daily), or placebo. 16 (2.1%) patients treated with nadroparin had a thromboembolic event versus 15 (3.9%) of those who received placebo (interim adjusted p = 0.033). The highest rates of thromboembolic events were associated with lung and pancreatic cancers, leading the investigators to conclude that future confirmatory studies should focus on these high-risk groups.

Statins and rituximab

Data from the Lymphoma Spore Registry suggest that statin use does not interfere with rituximab efficacy. Between 2002 and 2007, 293 patients with follicular lymphoma (FL) and 228 with diffuse large B-cell lymphoma (DLBCL) were prospectively assessed to see if statins inhibit rituximab binding to CD20. 19% of patients with FL patients and 22% of those with DLBCL were on statins at diagnosis; 16% and 19%, respectively, received them during treatment. At 36 months, statin use at diagnosis was associated with improved event-free survival for patients with FL (HR 0.57 [95% CI 0.34–0.95], p = 0.03) but not for patients with DLBCL; no significant effect of statin use was seen in patients with either disease who took statins during treatment.

Activity of fostamatinib

A phase II study of fostamatinib disodium, an oral inhibitor of Syk tyrosine kinase, suggests that the drug has clinical activity in DLBCL and chronic lymphocytic leukaemia (CLL). Jonathan Friedberg (Rochester, NY, USA) and colleagues tested the drug in 68 patients who had received a median of five prior therapies. The drug produced complete or partial responses in five (21%) of 23 patients with DLBCL, six (55%) of 11 with CLL, one (11%) of nine patients with mantle-cell lymphoma and two (10%) of 21 patients with FL, with a favourable toxicity profile.

Lenalidomide for lymphomas

Oral lenalidomide offers a viable treatment option for patients for diffuse large B-cell lymphoma (DLBCL) failing previous therapies, according to results presented by Myron Czuczman (Buffalo, NY, USA) and colleagues. In a phase II study in patients with relapsed or refractory aggressive non-Hodgkin lymphomas, oral lenalidomide (25 mg once daily on days 1–21) was given to patients in 28 day cycles, until disease progression or toxicity. 21 (29%) of the 73 patients with DLBCL, who had received a median of three prior treatment regimens, had an overall response, with three (4%) reporting a complete response, 18 (25%) a partial response, and 11 (15%) with stable disease.

Chronic lymphocytic leukaemia

Two phase III studies show patients with CLL treated with rituximab combined with chemotherapy live longer without disease progression than do patients treated with chemotherapy. In the CLL-8 study, Michael Hallek (Cologne, Germany) and colleagues randomly assigned 817 patients with previously untreated CLL to receive either fluda-rabine and cyclophosphamide (FC) or FC plus rituximab (FCR). After a median observation of 25.5 months, progression-free survival for patients on FCR was 76.6%, compared with 63.3% for patients on FC (p < 0.0001, HR 0.59 [95% CI not reported]), although the difference in overall survival at 2 years was not significant. Treatment with FCR caused more instances of neutropenia or leucopenia than did FC, without increasing incidence of severe infections. In the REACH study, Tadeusz Robak (Lodz, Poland) and colleagues showed in 552 relapsed and refractory CLL patients receiving RFC, progression-free survival was 30.6 months versus 20.6 months for those receiving FC (HR 0.65 [95% CI 0.51–0.82]; p = 0.0002). While grade 3 and 4 adverse events were more prevalent in the RFC group than in the FC group (80% vs 74%), serious adverse events were similar (50% vs 48%).

Janet Fricker

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EUROFILE

Proposed new law on animal experimentation

After six years of consultation, the European Commission has drafted a series of changes to the European law governing the use of animals in scientific research. Intended to create a level playing field for both commercial and academic research, the proposal includes new measures governing ethical review of research projects and restrictions on the use of non-human primates.

The scientific grounds of the existing Directive (86/609/EEC), were founded over 22 years ago. Many are 'out of date', and 'open to interpretation' says the Commission. Member states have applied the law to different degrees, which has resulted in market distortion and economic problems.

In addition, the existing law does not include modern animal welfare and experimentation practices or ethical reviews and authorisations for research.

The new draft proposed in November 2008, aims to rectify the situation at project, establishment, national and European level.

At project level, it proposes evaluation of all research, unless the procedures are categorised as mild and non-human primates are excluded. The re-use of animals in experiments would be limited to cases where the second procedure is either mild or terminal. However, the Commission has not defined the severity categories and intends to do so only after the law comes into force.

For all research requiring non-human primates – and projects of over 12 months involving other animals – the Commission wants a compulsory retrospective annual review. This would assess the numbers, species and life stages of animals used and those needed for the following year; techniques and killing methods. A permanent and independent ethical review body would assist in refining all experiments, reducing or replacing the animals used.

The use of non-human primates would be limited to preventing, diagnosing and treating life-threatening or debilitating clinical conditions in humans. Their use would also be restricted to second generation animals born into captivity after the law comes into force. For macaque primates currently used to test certain cancer therapies, this would be seven years after the law's implementation.

Establishments conducting research with animals would be asked to provide non-technical summaries of projects and make these publicly available along with any retrospective assessments.

The Commission foresees one scheduled and one unannounced national inspection of establishments, every year.

At national level, member states would need animal welfare and ethics committees to advise competent authorities and permanent ethical review bodies of establishments on best practices. The creation of a network of these national committees would play a role in the exchange of best practice at European level.

The European Coalition for Biomedical Research (ECBR), a grouping of scientist associations set up in 2007 to scrutinise the legislation, broadly approves. 'What the Commission has done is taken the toughest bits of control from various countries and put them together. So they have been road tested,' says Mark Matfield, ECBR general secretary and scientific co-ordinator at The Association for International Cancer Research.

'THE PROPOSAL MAY ONLY ALLOWS YOU TO TEST ONE DRUG PER ANIMAL'

However the Coalition has concerns: 'If you have an animal with a rare cancer or an unusual type of tumour and you want to test a series of drugs, you can do it sequentially on the animal provided it causes minimal distress,' explains Matfield. 'The way the proposal is drafted, you may well only be able to test one drug per animal. This would take longer and increase the number of animals used which is potentially quite bad for both the science and animal welfare.'

Further: 'Quite appropriately, the Commission is proposing to classify experiments according to the severity of pain that an animal is subjected to,' he says. 'No one has a problem with this but these should be defined upfront and not after the event,' he says.

Another issue is the increase in the administrative burden. 'The retrospective reviews of projects on a yearly basis is novel. It is certainly more bureaucratic and will increase the time and effort and paperwork in dealing with red tape,' says Matfield.

A particular cause for concern in the cancer community is the proposed restriction on the use of non-human primates. 'To get a reasonable response, biological therapies for cancer all have to be tested on non-human primates. Testing on other animals doesn't yield a response,' explains Matfield. 'The way the proposal is drafted, they could only be used into research on life threatening or debilitating human disease – which might exclude many skin cancers.'

The breeding of second generation animals is also a point of contention. 'Nobody has yet shown that you can breed sufficient numbers of second generation colonies. You have to demonstrate this before setting a timescale to require their use', says Matfield. Further: 'They tend to have health problems such as diabetes, which would make them unusable for most experimental purposes'.

The European Federation of Pharmaceuticals Industries and Associations welcomes the harmonisation of practices. 'However, any new provisions in the legislation should be based on sound scientific evidence, and should not unnecessarily increase red tape,' says EFPIA director general, Brian Ager.

'THE COMMISSION HAS PUT TOGETHER THE TOUGHEST CONTROLS FROM VARIOUS COUNTRIES'

The text has already been sent to the Council of Ministers and the European Parliament for revising and adoption. The process will take the best part of year if not longer. Matfield is optimistic on the outcome. 'These issues still need work but they can be fixed,' he says.

Saffina Rana
Brussels

Mandate for change in lung cancer

Lung cancer specialists have joined forces with psycho-oncologists to call for major changes in the provision of emotional support for lung cancer patients. They have signed a *Mandate for Change* which highlights basic rights for patients in terms of emotional wellbeing and quality of life.

The *Mandate* states that all lung cancer patients have the right to: feel empowered through knowledge about the choices available to them following diagnosis; information and resources that meet their specific needs which can be referred to in their own time; and access to psycho-oncology care as part of their ongoing health management.

More than half of all patients with advanced lung cancer experience anxiety and depression, research has found (*Support Care Cancer 2007;15(10):1207–12*). Professor Hellmut Samonigg (University of Graz, Austria) said, 'We need to create better emotional support systems to help lung cancer patients to manage their disease and improve the quality of their lives.'

A statement from the International Psycho-Oncology Society (IPOS), which is promoting the *Mandate*, notes that the aim is for each of the signatories to lobby in their home countries for the principles outlined in the document: 'How they do this depends on the individual signatory. Some will first make changes in their individual hospitals, some will lobby for changes in the medical societies and some will lobby for changes at country level.

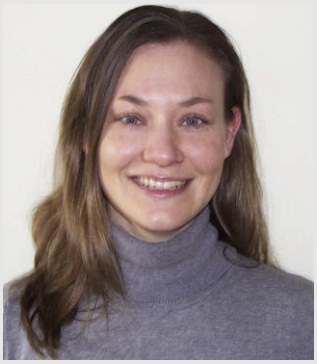
'An approach to the EC has not been ruled out,' the statement concluded.

Left to right: Dr. Antonio Sanchez (Hospital Peurta de Hierro, Madrid, Spain), Professor Jean-Francois Morere (University Paris XIII, France), Dr. Enrica Capelletto (San Luigi Hospital, Turin, Italy), Dr. David Heigener (Krankenhaus, Grosshansdorf, Germany), Dr. Luzia Travado (Hospital San Jose, Lisbon, Portugal), Professor Hellmut Samonigg (University of Graz, Austria), Dr. Martin Flicker (Leoben Hospital, Austria), Dr. Susana Rodrigues (Portuguese Institute of Oncology, Lisbon, Portugal), Dr. Lionel Bosquee (CHU Sart-Tilman, Liege, Belgium)

New publisher for EJC

Ms Sarah Jenkins has taken over from Dr. Peter Harrison as publisher of *EJC*. Dr. Harrison has been promoted to publishing director of Elsevier's health sciences journals division in the UK and will continue to oversee the journal indirectly.

Ms Jenkins has worked for Elsevier for seven years, initially as an administrative editor and more recently as a publishing editor. For a period 3 years ago, she managed *EJC*'s Special Issues and is looking forward to re-joining the journal. "I'm delighted to be working with John Smyth and the editorial board again. *EJC* has enjoyed enormous success over the last few years under John and Peter's leadership and I will be working with the team to continue this.



Ms Sarah Jenkins

'*EJC* is a multidisciplinary journal which aims to publish the best research from within Europe. It is widely read around the world and its rising impact factor demonstrates how valuable its content is.'

Dr. Harrison said, 'Working with the *EJC* editorial team over the past few years has been a pleasure and a privilege. I am sure that the journal will continue to develop further under Sarah's and John's management, and in collaboration with the editorial board and society partners.'

Extended indication for cetuximab

Cetuximab (Erbitux) has received European approval for its use to be extended to include first line treatment of patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck (SCCHN), in combination with platinum-based chemotherapy. The drug was previously approved for use in combination with radiotherapy for locally advanced disease.

Cetuximab is an IgG1 monoclonal antibody which inhibits the epidermal growth factor receptor, EGFR. Its most common side-effect is an acne-like skin rash, which can be severe.

The approval was based on the results of the EXTREME study (*N Engl J Med 2008;359:116–27*) which found an increase in median overall survival from 7.4 months among patients receiving platinum-based chemotherapy alone to 10.1 months among those also receiving cetuximab. Progression-free survival and response rates were higher in those taking both regimens.

PODIUM

Survival gap narrows in Europe

Dr. Riccardo Capocaccia (National Center for Epidemiology, Surveillance and Health Promotion, Rome, Italy) is a guest editor of EJC's forthcoming Special Issue on the EUROCARE-4 study. Some of the data was published in 2007; the Special Issue covers more cancer sites, giving a wider picture of survival in Europe, and provides commentary on its implications.

Why is there a need to keep on updating the EUROCARE figures?
Europe is changing, both politically, with new countries joining the EU, and medically, with improving diagnostics, access to care and better treatments. But expectations are also rising and we need to continuously monitor survival data to judge the reality.

What were the main findings from EUROCARE-4?
The EUROCARE-4 findings show marked and real differences in cancer survival across Europe, but the differences are narrowing. Absolute improvements were greater for countries which had lower survival rates in the past – in particular in the former Eastern Europe – than for countries where survival was already high. This is the first time we have seen a greater improvement in these countries than elsewhere.

We found the same trend within countries, typically in southern Europe, which have previously shown a high variability according to region. So Sicily and Sardinia have experienced a similar 'catch up' with northern Italy. In countries such as the UK and France, there is little variability in survival according to region.

How do you account for regional improvements?
Many health care systems are regionally-based, so that the level of expenditure and organisation is not uniform across the country. Improvements in survival rates are likely to be due to better organisation of services and perhaps more specialisation.

The Special Issue includes several new analyses?
Yes; it includes for example a paper estimating how many patients are cured of cancer. This is different from the 5 year survival figures which are usually published. Further, we used the new period survival technique to present up to date survival data. Usually, patients have to be followed for at least 5 years, but with this technique we can in principle provide 5 year period survival estimates one year after diagnosis. The information from this analysis is not directly comparable with conventional survival figures, and tends to underestimate the survival of recently-diagnosed patients. But it is useful and allows us to see the effects of new kinds of treatment much earlier.

We've also analysed subsets of patients, so we've compared survival in elderly compared with middle-aged patients, we've looked at gender, and specifically at children.

What are the implications of the still marked variations in survival across Europe?
We have to refine the data and collect more information on stage at diagnosis, the treatment given, and so on. This will allow us not only to observe differences in survival but also to explain them, to indicate the action needed and then monitor its effect. We need to understand, on a case by case basis, the best way forward, to bring all patients optimal care.

How far is survival linked with national expenditure on health?
There is some correlation, but it doesn't explain everything. It explains why survival is generally better in northern and some central European countries such as Germany and Switzerland. But countries with similar expenditures may have different survival rates. The health system and organisation of care is also important. The UK had relatively high expenditure and low survival in EUROCARE-3 but the differences, in breast cancer for example, have decreased in this study.

How does survival in Europe compare with that in the States?
The difference is probably narrowing. In prostate cancer, there is a much higher rate of early diagnosis through widespread use of the PSA test in the States, and very few aggressive cases. Overdiagnosis – of cases that would not have become clinically relevant – is much less common in Europe. There are indications that in other cancers, longer survival in the States is largely due to earlier diagnosis. In colorectal cancer, for example, diagnosis tends to be earlier in the US than in Europe, which leads to longer survival, but there's no indication that this is due to better treatment; it's greater efficacy of standard treatments, or even a longer lead time.

What needs to happen now?
In order to control cancer, we need to protect our registries; they cannot be taken for granted. The data is very important to the scientific community, yet, cancer registries are in jeopardy in many countries in Europe. EUROCARE-4 does not include data from some registries which were included in previous studies. Confidentiality, data protection issues, and uncertain funding have caused problems in several countries, including Estonia, Germany, Italy, the Netherlands, Slovakia, Spain, and the UK. Political activity on behalf of the registries has improved the situation in some countries, or we expect it will soon. In Italy and in some former East European countries, however, problems are ongoing.

Helen Saul