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ECCO 12

Sharp fall in prostate cancer deaths

Hormonal treatment for non-metastatic prostate cancer is as effective as tamoxifen in early breast cancer in reducing mortality, Professor Richard Peto (Oxford, UK) told delegates at ECCO-12 (Copenhagen, 21–25 September, 2003). 'It has been very much undervalued,' he said (*EJC Supplements* 2003; **1**, 5 #328).

Professor Richard Peto

In the US, prostate cancer mortality, which had been increasing slowly during the 1970s and 1980s, fell by one-third among men aged 50–74 years. "That decrease is going to continue," he said. Decreases are beginning to be seen in the UK, France and some other European countries and he said that, by 2010, national death rates will be half what they would have been without changes in management, such as the use of hormonal treatments, earlier diagnosis and better local control.

A meta-analysis included 5000 men with non-metastatic prostate cancer in trials of immediate versus deferred hormonal treatments such as orchiectomy or LHRH antagonists. Hormonal treatment was either given immediately or delayed by approximately 3 years from randomisation. All the treatments considered increased the avoidance of death from prostate cancer by roughly the same amount. "It works, about as well as tamoxifen works in breast cancer," he said.

Deaths from prostate cancer in the group receiving immediate treatment were 26% at 10 years compared with 38% in the group in which treatment was delayed. "Deferral is not a safe strategy," said Professor Peto. He said the effect was "absolutely definite and clearly real".

One agent, DES, turned out to be "seriously poisonous" and killed more people than it cured, mainly through an increase in heart attacks. This led to the mistaken belief feeling that prostate cancer mortality could not be altered by treatment. "The hazards of DES should be forgotten as we move on to other forms of treatments which do not have those life-threatening side effects," he said. The situation is "a lot more positive than had been supposed."

All-cause mortality was low and did not differ between the two arms (0.5%). "FOLFOX4 is the first combination to demonstrate superiority over 5-FU/LV in the adjuvant setting", she said. "If I had a stage III colon cancer, I would wish to receive oxaliplatin as adjuvant treatment."

Emma Cannell

Adjuvant oxaliplatin shows survival benefit

Colon cancer patients given adjuvant oxaliplatin show superior disease-free survival (DFS) to those on standard therapy, said Dr. C. Topham (St. Lukes Cancer Centre, Guildford, UK) presenting results at ECCO 12 (*EJC Supplements* 2003; **1**,5 #1085).

More than 2000 patients with completely resected stage II and III colon cancers were randomised in a multicentre, phase III trial (the MOSAIC trial). They received either 5-fluorouracil/leucovorin (5-FU/LV) treatment or the same regimen plus oxaliplatin (FOLFOX4) for 12 cycles. The primary endpoint was DFS.

Patients on FOLFOX4 had a significantly superior 3-year DFS (78% versus 73%) which translated into a 23% risk reduction in this group. Stage III patients showed the biggest benefit (72% versus 65%) while the corresponding results for stage II disease were 87% versus 84%.

There was more nausea, vomiting and neutropaenia in the FOLFOX4 arm, but a low level of febrile neutropaenia. Grade 3 sensory neuropathy was observed in about 12% of the patients on FOLFOX4, but this decreased to less than 0.5% 18 months after treatment. Alopecia and gastrointestinal toxicity were limited.

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Irradiation "does not cause second cancers"

Retinoblastoma patients given radiotherapy do not have an increased risk of second cancers compared with those who are not irradiated, according to Dr Jan Alsner (Aarhus University Hospital, Denmark).

Using data from 1943 to 2000, mainly extracted from the Danish Cancer Registry, children with non-hereditary retinoblastoma had a 5% risk of second cancers, which is similar to the 3% seen in the general population. (*EJC Supplements* 2003; **1**, 5 #721).

Patients with hereditary retinoblastoma had an increased risk of second cancers (15/88 cases; 17%), but this was associated with their *RB1* status and not with previous irradiation. In fact, although more than 70% of childhood patients are now 'cured', late effects - such as infertility following treatment with alkylating agents — are relatively common.

'Cured' patients might benefit from specialist late effects clinics, said Professor Jill Mann (Birmingham Children's Hospital, UK), but the clinics should be cost-effective (*EJC Supplements* 2003; **1**, 5 #724). 'Protocol-driven follow-up care is required so that we can audit and adjust the management we provide accordingly," she said.

Professor Mike Stevens (Royal Hospital for Children, Bristol, UK), former President of SIOP Europe, said, "SIOP Europe is working actively with the European parliament to raise these issues."

Emma Cannell

Predicting the response to 5-FU chemotherapy

Micro arrays may predict which patients with colorectal cancer will respond to chemotherapy, according to Professor Patrick Johnston (Belfast City Hospital, N. Ireland). He described use of the technology to identify groups of genes that may be involved in mediating colorectal tumour response to chemotherapy (*EJC Supplements* 2003; **1**, 5 #360).

Researchers identified a large number of genes that were upregulated by 5-fluorouracil treatment and found that these genes were also induced by raltitrexed and oxaliplatin (*Cancer Res* 2003 63, 15 4602–4606). Sample heterogeneity may be a problem in the routine use of these analyses, but access to the tumour tissues is likely to be more of a limiting factor, Professor Johnston said. "These drawbacks aside, we will have groups of markers that can predict response."

He said a study is underway at Johns Hopkins University, Baltimore, to examine whether, in stage II patients, micro satellite instability-high (MSI-H) and transforming growth factor B1RII status can be used to predict which patients will benefit from chemotherapy.

Emma Cannell

Molecular signatures in MALT lymphoma

Genetic rearrangements in mucosa-associated lymphoid tissue (MALT) lymphoma may help in understanding those cases that do not respond to *Heliobacter pylori* eradication, according to Professor Peter Isaacson (University College, London, UK), the recipient of the FECS Clinical Research Award (*EJC Supplements* 2003; **1**, 5 #1). He said three different translocations found in MALT lymphoma — referred to as molecular signatures — lead to the same molecular pathway, the NFKB complex, and could hold the key to further understanding.

These signatures should help us "to identify other relevant microbial agents allowing us to treat these lymphomas," he said.

Translocations were observed in t(1;14), t(11;18) and t(14;18). The t(1;14) translocation involves the Ig heavy chain and the pro-apoptotic gene *bcl-10*, resulting in increased nuclear expression of the BCL10 protein. The t(11;18) translocation involves genes encoding the apoptosis inhibitor *API2* and *MALT1*. The t(14;18) involves IG heavy chain gene and the MALT1 gene leading to overexpression of *MALT1*. BCL-10 interacts with MALT1 causing it to dimerise and signal to the NFkB complex.

Thus, these translocations all modulate the same NFkB pathway through direct or indirect effects on the *MALT1* gene.

Emma Cannell

TFIIIB at the "centre of a battleground"

The transcription initiation factor, TFIIIB, becomes a target in transformed cells, according to Professor Robert J. White (Glasgow, UK), winner of the EACR award at the ECCO 12 conference. "TFIIIB is at the centre of a battleground. . . and a host of oncogenic factors act to subvert its control" (*EJC Supplements* 1, 5 #6).

TFIIIC and TFIIIB recruit RNA polymerase (pol) III and position it to allow transcription. In untransformed cells, repression of TFIIIB may help to restrain cell growth. However, in tumours, pol III levels are raised. Professor White suggested this may provide sufficient tRNA and 5S rRNA (products of pol III activity) to sustain the increased protein synthesis rates necessary for tumour growth.

Several tumour suppressors act as repressors of pol III transcription. It has been proposed that the function of the retinoblastoma protein, Rb, is compromised in all tumours. Rb-compromising mechanisms include phosphorylation, binding to viral oncoproteins and mutations in the Rb pocket domain - all of which have been shown to result in increased pol III transcription. Rb binds and represses TFIIIB preventing its interaction with pol III and TFIIIC. Pol III transcription is also repressed by another tumour suppressor, p53, again through binding to TFIIIB. Loss of p53 function can depress TFIIIB and increase pol III transcription.

Oncoproteins, such as c-myc, also bind to TFIIIB and can act to directly stimulate pol III transcription. A network of regulators therefore acts on TFIIIB tumour suppressors to restrain growth and oncogenic factors to subvert growth control, he said. It appears that cancer cells are keen to achieve a high pol III output, but it remains to be seen whether the pol III system will be a useful therapeutic target.

Emma Cannell

Professor White describes his research in more detail in a Review published in this issue.

EUROFILE

Hope fades for major public health projects

High-level protests directed at the European Commission's Public Health Directorate (DG-Sanco) have fallen on stony ground. DG-Sanco's recent decision not to continue funding major cancer projects has attracted criticism from members of National and European Parliaments. However, the decision is unlikely to be reversed.

Projects affected include the European Prospective Investigation into Cancer and Nutrition (EPIC), the European Network of Cancer Registries (ENCR), European Breast Cancer Network (EBCN), European Cervical Cancer Screening Network (ECCSN) and the Eurocare Study. EUROCHIP-2 on health indicators, and two smoking-related projects were funded.

EC Commissioner, Mr David Byrne received letters of protest from Belgian and German Ministers of Health and German member of European Parliament, Ms Karin Jöns, who is also President of Europa Donna Germany, and Chair of the European Parliamentary Group on breast cancer (as noted in *EJC 2003 39, 2415–2416).* In his reply to Ms Jöns, Commissioner Byrne stated that the Cancer Networks did not fit into the Commission's priorities for the 2003 work plan.

"THE SITUATION IS KAFKAESQUE"

The projects are of "good technical quality", he wrote, but there was "overwhelming over-application" for funds in the 2003 programme. "A massive investment has taken place over the last 15 years in cancer prevention in comparison with other major public health issues. Cancer epidemiology is the most developed area of health statistics, and . . .the question arises as to whether . . . we need to focus some of the limited resources in areas where the situation is at a critical embryonic stage, like cardiovascular diseases, diabetes and mental health."

Ms Jöns said, "It's now clear there is no chance we can modify the 2003 selection process. What's important is to get the cancer networks into the 2004 work plan, to open a door for them to continue. We need them for the implementation of the Council Recommendation on cancer screening."

A meeting of the EPIC Steering Committee took place in October 2003, and decided that, in the short term, the project would continue with funds from national sources and some emergency funds that have been found. Dr Elio Riboli, European coordinator of EPIC, said, "It was a good meeting. The researchers are motivated to go on working, there is strong solidarity and we are fighting to continue to do good research. But we are deeply disappointed."

The meeting decided to apply for money from the EC in other ways, such as for a small grant supporting the coordination of research. It will also apply for grants from the US National Institutes of Health (NIH) — it has received NIH grants in the past. "If there is no possibility of European funding we will go elsewhere. We cannot sit on the data we have. EPIC has now accumulated precious data on over 25 000 cancer cases we have published more than 100 scientific manuscripts and have many more in preparation," said Dr Riboli.

"REGISTRIES ARE NOT POLITICALLY ATTRACTIVE"

Commissioner Byrne suggested that EPIC apply for funds from the EC's Research Directorate, DG-Research. However, Dr Riboli said, 'The situation is Kafkaesque. The 6th Framework Programme is divided into hundreds of very specific titles. If your area of research doesn't fit one of the titles, you can't apply. Unfortunately among the titles relating to cancer focus on clinical research and genetics, there is nothing on epidemiology, and the only item that refers to nutrition in cancer is for research into environmental chemicals in food, such as acrylamide. There is nothing on general nutrition, diet and cancer. It is not that they won't fund us; we can't even submit an application.'

Dr Max Parkin (International Agency for Research on Cancer, Lyons), European coordinator of ENCR, said that relevant staff at IARC have already been given their notice. The ENCR Steering Committee was due to meet in mid-December 2003. Dr Parkin said, "We may have an indication by then whether our application will be viewed more sympathetically in 2004. We may be able to keep going on a shoestring for 9 months or so, to plug the gap, but without proper funding there will be no major activity beyond that."

Dr Richard Sullivan, Head of Clinical Programmes at Cancer Research UK, said there is a tension in Brussels between wanting to fund excellent basic science, and funding science that cannot be funded at the national level. "The bottom line, in our view, is that Europe should be supporting research that cannot be supported in any other way. If it is serious about patient benefit, it should put money into the big epidemiology networks, into research on orphan diseases such as childhood cancers where there are too few patients to conduct studies at a national level, and the big trial networks. These can not be funded at anything other than the European level."

Fashions in research often hold sway in Brussels over continuity of funding, he said. Furthermore, "Cancer registries are not politically attractive, but they are absolutely necessary for making good policy decisions."

He said that applying for European money was time-consuming and complex for researchers. "There needs to be absolute transparency. If Brussels wants to fund big basic projects, it needs to tell clinicians and epidemiologists not to bother applying."

Helen Saul

Awards at ECCO-12

New methods for planning and delivering radiation oncology will have to be tested in randomised controlled trials (RCTs), according to Professor Søren Bentzen (University College, London). Receiving the European Society for Therapeutic Radiology and Oncology (ESTRO) Klaas Breur Award, he said that improved dose-distributions only convince fellow radiation oncologists. "What is required for rational progress is evidence from RCTs that outcome is improved in the clinic," he said.

Professor Bentzen received the award "in recognition of his distinguished contribution in the field of radiation on oncology and his continuous support of ESTRO actions." He trained at University of Aarhus, Denmark, before moving to London, and his research interests include translational radiation oncology including predictive and prognostic factors; biological optimisation of radiotherapy and combined modalities; and evidence-based oncology. He is working on the incorporation of data from genomics, proteomics and functional imaging into novel strategies for radiation therapy.

In his award lecture, he described improving methods of spatial modulation of radiation and progress in functional and molecular imaging. These techniques will allow detection of variations within the tumour, such as hypoxic areas and the distribution of markers and make possible three-dimensional "dose painting by numbers". Radiation will be "prescribed" according to the function of the tumour, not its anatomy alone, he said.

Prognostic and predictive factors, such as receptor expression, will allow the selection of subsets of patients who would benefit from one type of therapy rather than another; and determination of the optimum intensity of treatment. "The clear challenge we face is to translate progress into improved care for cancer patients," he said.

Professor Alison Richardson (King's College London, UK) was presented with the European Oncology Nursing Society (EONS) Distinguished Merit Award "as a recognition of her efforts to further the speciality of cancer nursing". Professor Richardson trained in nursing at the Welsh National School of Medicine and specialised in cancer nursing at the Royal Marsden Hospital. She gained an MSc and PhD and now holds the Chair in Cancer and Palliative Nursing Care at King's College, London.

Her lecture, 'Creating a culture of compassion: developing supportive care for people with cancer,' called for more rigorous symptom assessment and documentation, better management of the symptoms and concerns that confront people with cancer, and a more integrated approach. She called for "a dedicated infrastructure of staff and services" and said, "Nurses must play a key role in supportive care."

The importance of supportive care was also stressed by **Professor Hans-Jörg Senn** (Zentrum für Tumordiagnostik und Prävention, St Gallen, Switzerland). He won the **Pezcoller Foundation/FECS Award** for "outstanding work in the field of oncology through far-sighted advanced interdisciplinary care of the cancer patient."

Professor Senn established the first comprehensive cancer centre in Switzerland, at the Kantonsspital St Gallen. He is an expert counsellor for the German Ministry of Science and Technology in Bonn, and he established the German-speaking branch of the European School of Oncology (ESO) in 1997. He is a former Editor-in-Chief of *EJC*.

In his award lecture, he said that supportive care in cancer had evolved over the past 15 years as a "silent paradigm shift" in which a patient's well-being, regardless of the eventual outcome of treatment, has become "an important, independent outcome of care."

Professor Peter Isaacson (University College London, UK) won the **FECS Clinical Research Award** "as a token of his outstanding contributions to oncology in general and to haematopathology in particular". Professor Isaacson and his group have worked to determine the MALT lymphoma concept (*see* "Molecular signatures' story, p?).

Professor Bob White (Glasgow, UK) won the **European Association for Cancer Research (EACR) Young Cancer Researcher Award** "in recognition of his contribution to understanding how tumour suppressor genes and oncogenes control the synthesis of small RNAs by RNA polymerase III" (see "Centre of a Battleground" story, p?). Professor White trained at Oxford and London, and worked in Cambridge before moving to Glasgow to set up his own lab. He became Professor of Gene Transcription at Glasgow University at the age of 35. His work has demonstrated unexpected links between pol III and key growth controllers that can explain the hyperactivity of pol III in cancer cells.

The European Society of Surgical Oncology (ESSO) Award went to **Professor Luigi Cataliotti** (University of Florence, Italy) "in recognition of his far reaching achievement in the field of breast cancer and his outstanding international contribution to harmonise the quality of patient care in Europe and increase contacts between scientists interested in breast cancer." His main research interest is breast cancer and his research projects include non-palpable lesions, ductal carcinoma in situ, quality control in the diagnosis and treatment of breast cancer. He is President of EUSOMA, President Elect of ESSO, and a member of the EORTC's Steering Committee on Breast Cancer.

Professor Hansjörg Riehm (Hannover, Germany) received the **SIOP Europe Award (European Branch of the International Society of Paediatric Oncology)** for his "outstanding contribution to paediatric and adolescent oncology". Professor Riehm trained in medicine and paediatrics in Berlin, and was head of Paediatric Haematology and Oncology in Hannover for 13 years. He was one of the pioneers of multidrug chemotherapy in acute leukaemia, at a time when it was generally considered that children could not tolerate multi-agent therapy, and that it was unethical. "In retrospect, even in these early days, sufficient powerful drugs were available in order to imagine drug combinations with a curative outlook," he said.

The winners of the FECS-EJC Awards—Dr Cai Grau (Aarhus University Hospital, Denmark), Professor Alex Eggermont (EORTC Melanoma Group, Belgium), Mr M Johnson (King's College, London) and Professor Bengt Glimelius (University Hospital, Uppsala)—were reported in *EJC* News, issue 17, 2000.

PODIUM

Tissue banks: who decides what is ethical?

Dr Manuel Morente is Director of the Spanish National Tumour Bank Network at the Centro Nacional de Investigaciones Oncológicas (CNIO) in Madrid. It is the first such Network in Europe. Dr Morente is an advisor for emerging Tumour Bank Networks in Europe and Latin America, and is involved in the EORTC's TUBAFROST project. He collaborates in projects about molecular profiling of cancer and its clinical value, mainly in Hodgkin's lymphoma.

Dr Manuel Morente

Where is the Spanish National Tumour Bank Network located?
The samples themselves are held in Spain's 17 major public hospitals. We coordinate the Network at the CNIO, promoting quality assurance. All hospitals use the same technical and ethical protocols, and the office here keeps a database detailing the tissue samples. Samples always travel through the central office in order to preserve confidentiality. They are identified by a code in the central database, but patient information is held at the hospital only and samples are passed on to researchers without identification data.

How active is the Network?
The CNIO is a young centre; it has been running less than 4 years. Our Network has already participated in 100 scientific projects, many of which have appeared in high quality journals. Furthermore, at CNIO we are developing our own monoclonal antibodies and tissue micro arrays, and the Network supplies high quality frozen and fixed tissue samples. This time-consuming work does not always appear in research papers, which is frequently the only measure of scientific work. Tumour banks are the nuts and bolts of translational cancer research, but they are largely invisible.

Do you participate in international research?
We do and it is difficult in Europe. Our American colleagues have clear regulations. In Europe we live in isolation from one another. The Nordic countries have strict regulations that make collaboration with other European countries difficult.

In the rest of Europe, national regulations differ only by nuances. We have no major problems collaborating with the Netherlands, the UK or Italy. But in some hospitals, patients are asked to decide whether their sample can be used for research into their disease only, or into any disease. This creates an extra hurdle as we have to check what consent was given, but it is manageable. But it is an absurd distinction, especially as a new taxonomy of the diseases is emerging based on molecular profiles.

How strict are the ethics governing your work?
Too strict. The whole field of ethics is in the hands of experts in law and philosophy, rather than in science, and because of this, the distinction between different types of projects—for instance, clinical trials versus preclinical research, or tumour banks versus gene banks—often gets lost. Clinical trials, which may provoke a change in patients' treatment or management, clearly need to be governed by strict ethics. The situation is quite different in basic research, which uses anonymous samples linked only by a code to a patient's clinical file, which is not available to the researcher. This research does not provoke a change in patients' treatment or management; they are not identified except by a code and so the research does not require project-specific informed consent. Ethics committees should look at the final use made of the sample in biomedical research. The public is in favour of this research and is sometimes not well served by these committees of experts.

Would you like to see new regulations governing the whole of Europe?
Obviously we need new regulation to harmonise the laws governing tissue banks and laboratory work across Europe. But I'm afraid that, because the laws would be drawn up and debated by politicians and people who do not have a scientific point of view, new legislation might make things worse. The European Directive on Clinical Trials is a case in point. It could damage clinical trials promoted by academia and we not want the same thing happening to preclinical research.

Bioethics is thought to be a new way of controlling biomedical activities, but doctors have been making hundreds of ethical decisions every day for centuries with no major scandals.

What would you like to see happen?
We need a forum for discussion in which all viewpoints are represented: law, philosophy, research (both managers and researchers), patients and the general public. The public should be involved because they are future patients—a point of view which is never mentioned. Ethics in biomedical research is a question of balance between the rights of current and future patients.

How optimistic are you that existing barriers will be removed?
I am intrinsically optimistic. In science, every new step creates difficulties but new solutions always appear. For instance, the development of virtual pathology, which would mean that data, rather than samples, are sent, may be a way round. It is difficult and expensive, but may be necessary in order to allow this work to continue.