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'New guidelines required' for halting trials early

A leading breast cancer specialist has urged researchers to consider changing the guidelines that govern whether clinical trials should be stopped early. Dr. Martine Piccart (Institut Jules Bordet, Brussels, Belgium) believes that current practice could be damaging research efforts.

''QUESTIONS ABOUT LONG-TERM EFFICACY REMAIN UNANSWERED''

Speaking to *EJC* at the 4th European Breast Cancer Conference in Hamburg (EBCC-4, 16–20 March 2004), she said that breast cancer research has not been well served by early reporting of results. For example, the recently halted aromatase inhibitor (AI) trials, aimed at preventing recurrences, may have left questions about long-term efficacy and side effects unanswered. Furthermore, the future of other trials could be put at risk.

''Researchers need to achieve a better balance between informing doctors and women quickly about a more effective treatment for breast cancer and the equally important need to collect solid data on the safety of the therapy,'' she told a discussion group at the Hamburg conference.

''I suggest that guidelines should be drawn up and agreed by the research community, whereby early disclosure is based on significant differences between the rates of distant relapse. Distant relapses mean the cancer recurring in lung, liver or bone, for which there is almost no chance of cure, in contrast to relapses in the breast and regional nodes for which curative therapy exists''.

Dr Martine Piccart

Dr. Piccart warned that big questions remain about the long-term effects and effectiveness of newer adjuvant therapies such as the AIs, and she urged physicians to make ''individualized'' treatment decisions with their patients.

''Although there have been several trials now that show positive results for AIs, the long-term effects are still unclear. Questions remain about their effect on bone and cardiovascular health, cognitive and sexual function, and quality of life'', she said. ''The biggest question is which will be the optimal new endocrine therapy: an AI upfront instead of tamoxifen or a few years of tamoxifen followed by an AI? Also, should the AI be given for two or three years, or for five years, as is now current practice with tamoxifen? At present no-one can say what is the best treatment strategy for AIs''.

As a result of the discussion at EBCC-4, BIG has agreed to set up a working committee to discuss the premature stopping of clinical trials in more detail and draft a position paper. Dr. Carolyn Straehle, managing director of BIG, told *EJC* that the BIG working committee would comprise clinicians, statisticians and a patient advocate. ''Because of potential cultural differences in attitude toward the subject, the preference was first to come to some type of consensus within BIG (predominantly European) before meeting with the US Breast Intergroup. We are all agreed that it is very important to be in dialogue with them over this issue''.

Emma Mason
Hamburg

Mammography for all!

All European countries should introduce mammography screening for women aged 50–69 in accordance with the EU guidelines, according to MEP Karin Jöns, the European Parliament's standing rapporteur for breast cancer. At EBCC4's opening ceremony, she said they should also establish a multi-disciplinary breast unit for every 330,000 inhabitants.

Ms Karin Jones

These conditions, which must be in place by 2008, she said, apply also to the eastern European countries which joined the EU in May 2004. The European Parliament and Commission will first take stock of the situation in 2006. 'The then 25 Member States will have to show whether they have actually made progress in the early detection and treatment of breast cancer', she said.

Other sessions at the conference addressed the difficulties of achieving this goal, particularly in countries with limited resources. Speakers highlighted problems not only in funding mammography screening, but also in training and retaining enough properly qualified radiologists to read the mammograms, and in encouraging women to attend for screening.

Conference chair, Professor Jacek Jassem said the meeting was extremely successful, and had a ''high scientific level, outstanding lectures, perfect organisation and last but not least – friendly atmosphere. I very much enjoyed the lively sessions with active interaction from the floor, breaking all speaker-audience barriers. Now, we have challenged the chair of the next EBCC''.

Emma Mason
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Tobacco fights back

Researchers are using genetically-modified tobacco plants to produce a vaccine against cervical cancer (Science in Africa, March 18, 2004). Cervical cancer associated with human papillomavirus (HPV) is the leading cause of cancer death in southern Africa, where the disease afflicts mainly poor women with ''limited access to cervical-screening programmes, who will also most probably not benefit from the [more] expensive vaccines under development'', comments Ed Rybicki, University of Cape Town, South Africa.

Transgenic plants have several benefits: expression of vaccines in these plants eliminates the risk of contamination with animal pathogens, provides a heat-stable environment, and avoids, if administered as an edible vaccine, injection-related hazards. Furthermore, edible plants can be grown locally and distributed easily without special training or equipment.

Rybicki's group generated papillomavirus virus-like particles (VLPs) from the major capsid gene L1 in transgenic tobacco (*Nicotiana tabacum*), and showed that the particles had antigenicity and immunogenicity. In these experiments, done with an HPV type-16 L1 gene derived from a South African patient sample, the genes were stably integrated into the genome of *N tabacum*, and the expressed proteins could assemble into capsomers and VLPs. In another study, with HPV type-16, an L1 sequence was introduced into tobacco and potato, and the plant expressed L1 self-assembled into VLPs with immunological properties comparable to those of native HPV virions. ''We are quite far along in showing equivalence of our product with the 'gold standard' baculovirus-produced VLPs'' says Rybicki (baculovirus expresses papillomavirus capsid proteins in insect cells and produces HPV VLPs). ''What remains for us to do'', he notes, ''is to improve the fairly low yield of VLPs per kilo of tobacco leaves''

Rybicki's work has been funded by the National Research Foundation of South Africa's Innovation Fund – a competitive grant aimed at stimulating development of new projects through to the brink of commercialisation.

Rybicki says that the advantages of their approach are production of a vaccine via an inexpensive and scalable resource, and the fact that ''all the work in establishing the suitability of such vaccines produced by more conventional routes will already have been done by big drug companies by the time we conceivably get there, which should lower the regulatory hurdle''.

Rybicki adds: ''We hope to show the international community that it is possible to do such work in a developing country and that there are alternatives to waiting for big drug companies to produce vaccines that may never be cheap enough for the people they would most benefit''.

Xavier Bosch

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RNAi in human screens

RNA interference (RNAi) – a tool that silences genes – has been used by Dutch researchers in large-scale mammalian screens for the first time. The work will take our understanding of mammalian gene function 'a further giant stride forward', a commentator said.

The Dutch group, led by Dr. Katrien Berns (Netherlands Cancer Institute, Amsterdam), used the technique to help dissect critical cellular pathways. ''Our data highlight the power of large-scale RNAi screens in mammalian cells'', they reported (*Nature* 2004; **428**: 431–37).

''WE WILL SEE AN EXPLOSION IN RNAI SCREENING''

RNAi – the use of double-stranded RNA (dsRNA) to silence genes – has been useful in dissecting pathways in lower organisms such as nematodes and flies. The length of the dsRNA has limited its use in humans as it provokes an anti-viral reaction when introduced to the cell. Smaller short hairpin RNAs (shRNAs) have therefore been designed. These are synthesised in the cell into small interfering dsRNAs (siRNAs) that are small enough to avoid immunological attack. siRNAs suppress gene expression in human cells.

Dr. Berns and colleagues used the technology to identify genes affecting p53 function – a tumour suppressor gene that is commonly deregulated in human cancer. Five new modulators of p53-dependent cell arrest were identified.

In the same issue (*Nature* 2004; **428**: 427–31), a US group also generated a retroviral-based shRNA library to screen human genes. Dr. Patrick J. Paddison (Cold Spring Harbor, New York) and colleagues targeted a similar number of genes to Berns' study – almost 10,000 – and validated their library against a genetic screen reporting defects in human proteasome function. ''The availability of this resource to the research community will open the door to the use of RNAi in mammalian systems as a large-scale tool for biological discovery'', they reported.

Commenting on the work, Dr. Andrew Fraser (Wellcome Trust Sanger Institute, Cambridge, UK), agrees. ''We will no doubt see an explosion in RNAi screening of mammalian cells over the coming months'', he said (*Nature* 2004; **428**: 375–77). Such libraries could screen every gene in the human genome for a particular process and ask if it is involved. However, both specificity and the efficiency of targeting are areas of uncertainty in the future use of this technology, he said. ''Like any screening tool, RNAi is unlikely to be perfect. As the rules for predicting effective shRNAs continue to improve…the libraries will improve.… Pulling together the data from these varied RNAi screens in a common database will take our understanding of mammalian gene function a further giant stride forward'', he concluded.

Emma Cannell

For further information, see the review on the use of RNA Inhibition by Professor Finbarr Cotter, London, UK. It will be published in a forthcoming issue of EJC.

EUROFILE

European patients find a voice

The European Patients' Forum (EPF), formally launched at the European Parliament in March 2004, is a milestone in the rise of the patients' movement. European patients are, finally, represented by a single voice.

The patients' movement in Europe still trails behind its counterpart in the US, which is a force to be reckoned with. It has roots in the women's movement and its basic premises were outlined in the 1970s classic 'Our bodies, ourselves'. Later, the movement was bolstered by the emergence of the well-informed and politically active HIV patient. Over the last 40 years, US healthcare consumers have been instrumental in bringing about any number of changes across the Atlantic, from quicker access to innovative medicines to involvement in clinical trial design.

European patients began to wake up to the possibilities for improving their lot in the 1990s, but the EPF only came into being in 2003, a few months before its formal launch. The group aims to represent the views of patients in all European countries and with all kinds of conditions, and to promote the patient perspective in both national and pan-European debates on healthcare systems.

''RESPONDING TO CONFLICTING INTERESTS IS A CHALLENGE''

The European Commission has long been calling for the development of such a Forum. The lack of a single voice representing patients at European level has caused Commission officials many problems; they have struggled to find representative groups to discuss proposals with, and as a result, have sometimes been accused of being insufficiently sensitive to the patient point of view. ''Having patients' voices heard is now crucial'' said Dr. Fernand Sauer, Director for Public Health, DG Sanco, at the launch of EPF. ''Today's citizens do not only want to have more information than before. They also want to see their experiences, opinions, and priorities reflected in health policy making. Responding to these various, sometimes conflicting, interests is a challenge for policymakers and also for civil society''.

Mr. Rodney Elgie, President of the Patients Forum, was upbeat about what could be achieved. Patients are the real experts in their disease, he said, and only they really know what works well and what does not. They are aware of the problems of living with their condition, and what their priorities are. ''Health professionals and politicians may have different priorities which can lead to less effective treatment and incorrect prioritisation'', he said. ''Inappropriate use of resources leads to wastage and less effective or fewer treatments for others. Good health should be viewed as an investment, not a cost.

''PATIENTS ARE THE REAL EXPERTS IN THEIR DISEASE''

''There is a view that the educated and informed patient will lead to an explosion in demand for modern and high cost prescription-only drugs'' he said, ''but this has yet to be proved. One thing we do know is that medication is infinitely cheaper than hospitalisation''.

Patients are not just there to help themselves, said Mr. Elgie. They could be an effective tool for the education of all European citizens on, for example, the value of early and correct diagnosis to improve outcomes for patients and minimise costs to health authorities. ''The real key is to engage people in their own health management'', he said. Good practice needs to be shared, and patients are the ideal vehicle for promoting messages.

In a statement endorsed by European doctors and nurses organisations, the European Patients Forum says: ''All patients, no matter what their condition, background or nationality, have a fundamental and legitimate human right of access to all kinds of knowledge about their health, medical conditions and the availability of treatments including knowledge of the best available management for their disease. They need to understand their condition and to be able to receive information on genetic and hereditary factors, where relevant, and on all available treatments. It is a question of solidarity, equity, and patients rights''.

Members of the EPF are organisations representing people with chronic disease, which present the greatest of all challenges to national governments. But people with acute disease are equally in need of representation, and up to now this has been lacking. There are obvious reasons for this – when someone is acutely ill they are unlikely to have the energy to worry about political activity – but their lack of representation leaves a gap that needs filling.

The EPF intends to do its best for all patients, though. It says that simply allowing individuals the fundamental right to knowledge about their health, available treatments and disease management strategies would make a huge difference to quality of life for everyone. Compliance would be improved if patients understood more about their treatments and why they are taking them; awareness of the risks and benefits of prescription medicines and the importance of reporting and managing possible side effects would also improve; quality of life would be better with the taking of preventive measures, eliminating risk-taking activities, recovering more quickly from illness, and avoiding hospitalisation and invasive surgery.

This may sound hopelessly utopian, but experience of patient power elsewhere has shown that it can lead to real benefits for all sides. The Patients Forum has made the first move at European level. Let's see what happens next.

Mary Rice
Brussels

10 years of Europa Donna

Europa Donna – the European Breast Cancer Coalition – marked its 10th anniversary with a cocktail reception at the 4th European Breast Cancer Conference in Hamburg (EBCC-4, 16–20 March, 2004). The education and advocacy group celebrated the accomplishments and progress it has made in raising public awareness of breast cancer and in advocating equal access to standardised services and best practice for all European breast cancer patients.

Conference co-chair and past president of Europa Donna, Dr. Mary Buchanan, said: ''Major achievements include the launching of the annual Europa Donna European Breast Cancer Advocacy Course for the ongoing training of breast cancer advocates in Europe, and successful parliamentary lobbying which at the European Parliament placed breast cancer firmly on the European health care agenda. This had two important outcomes – the Resolution on Breast Cancer passed in the European Parliament in June 2003 and Europa Donna's involvement from the outset in the European Health Forum and in the establishment of the European Patient's Forum.

''Europa Donna thanks all its friends and colleagues for their support and encouragement and looks forward eagerly to working with them through the next 10 years and beyond. The women's voice in breast cancer advocacy in Europe will continue to be heard through Europa Donna.''

Dutch couple win Nathwani prize Huub van der Lubbe and Teuntje Klinkenberg receive the Nathwani Prize from Dr. Mary Buchanan

The conference also celebrated the contributions of two individuals touched by breast cancer, when the Nathwani Prize was awarded at the conference opening ceremony to a couple from The Netherlands.

The award is made every 2 years to those whose work best embodies the link between medicine and humanities in the quest for improvements in the length and quality of life for patients with breast cancer. Teuntje Klinkenberg, a stage director and producer, has written, directed and acted in a performance based on her experiences and emotions as a breast cancer patient, survivor, wife and mother. Her husband, Huub van der Lubbe is a singer and writer with a Dutch rock band who has written songs and poems based on his emotions as the partner of a breast cancer patient.

Dr. Buchanan said: ''After the presentation of the prize, Teuntje and Huub gave a moving performance in poetry, prose, music and song. This gave the audience a very tangible expression of the intended spirit of the Nathwani Prize.''

Emma Mason
Hamburg

French scientists' dispute settled

The French government has announced the restoration of 550 research posts and the creation of 1000 more university jobs in a move that has brought the crisis to an end (*Lancet 2004 363:1294*). A spokesman for the *Let's Save Research* collective, which represented the scientists, welcomed the decision. 'This is a great day for French research,' said Alain Trautmann.

The dispute started in 2003 with the introduction of large budget cuts in research. An Internet petition – *Let's Save Research* – was signed by more than 70,000 researchers and the action culminated in March 2004, when 3,500 senior researchers at major centres resigned from their managerial duties.

The petition demanded that the government come up with Euro 200 million owed to science agencies from past budgets; organise a national convention to map out the future of French science; and reinstate the 550 permanent posts in government laboratories which had been turned into temporary 3- or 5-year contracts.

Poor results in regional elections triggered a cabinet reshuffle, and an acknowledgement from President Jacques Chirac that funding was insufficient. The new Education and Research Minister, François Fillon, and delegated minister of research, François d'Aubert met the heads of the major research organisations and announced the problem solved.

Alain Trautmann said, 'It's exactly 3 months since the movement began on January 7th. 3 months on, we have obtained everything we asked for as urgent measures'.

Radioimmunotherapy product now available

A radiolabelled antibody has been made available in the UK for the treatment of a category of patients with non-Hodgkin's lymphoma (NHL). Ibritumomab tiuxetan (Zevalin) has been launched for the treatment of CD20 positive, follicular B-cell NHL patients who are refractory to or have relapsed following rituximab therapy.

The drug received EU approval in January 2004, and was, according to manufacturer Schering Health Care, the first approved radioimmuno- therapy in Europe. It combines an anti-CD20 monoclonal antibody (ibritumomab) with yttrium-90 radiation. The CD20 antigen is used as the target because it is expressed on more than 90% of B-cells in NHL and has a stable cell surface expression. It does not circulate freely in the plasma.

Treatment begins with an infusion of rituximab to deplete circulating CD20+ B-cells. On day 8, a second infusion of rituximab is followed by an intravenous injection of Zevalin. Lymphoma cells are radiation sensitive and it is hoped that Zevalin's beta radiation will penetrate even bulky tumours where blood supply is poor and destroy the inner part of malignant cell clusters.

PODIUM

From certain death to benign lumps: paediatric cancer transformed

Dr. Giulio D'Angio, Professor Emeritus at the University of Pennsylvania, USA, is regarded as the father of paediatric oncology. He was a founder of the National Wilms' Tumor Study (the first intergroup for a childhood cancer), the Late Effects Study Group, and the Histiocyte Society. He has received numerous national and international awards for his work.

Dr Giulio D'Angio

What drew you to work with children with cancer?

As a medical student, I saw a little girl who had a sarcoma that had broken through her skin. She was in a room on her own with the blinds down because of the foul smell; even her parents didn't want to visit. She is seared in my memory, she must have felt totally abandoned. I wanted to change things for those that followed.

When I graduated, in 1945, every child with leukaemia died within 6 months and the overall survival for children with cancer was 20% at best.

Why radiation therapy?

I was a surgical intern initially but switched to radiation therapy because in those days, only radiotherapy had the potential for cure. It was being used in adults, but not so much for children. They were seen rather begrudgingly as a side issue, because childhood cancers are comparatively rare. If the little girl with sarcoma had received radiotherapy, she would at least have died more gracefully.

What have been the milestones in paediatric cancer?

In 1903, the German surgeon G. Perthes showed that x-radiation interfered with normal growth and development. He irradiated one wing of chicks and noted their underdevelopment compared to unirradiated wings as the birds matured. It suggested that radiotherapy might destroy cancer, but might also lead to unacceptable long-term disability when given to children. Even decades later, this finding impacted strongly on my work.

I worked with Robert E. Gross, a dextrous and revolutionary surgeon, at the Boston Children's Hospital. He was a clinical scientist and never rushed in; he wanted to know the epidemiology, aetiology, basic pathology and physiology before going on to innovative surgery. He was enormously influential in showing that very large tumours could be removed from very small children safely.

Another extraordinarily important milestone came from the great pathologist Sidney Farber, with whom I also worked in Boston. Early observations suggested that a simple chemical like folic acid could induce remissions in cancers. In trials, though, it made the situation worse. Instead of giving up, Sidney Farber used this finding and worked with biochemists to develop an anti-fol. It was the first drug to produce remissions in children with cancer.

What has been your contribution?

I coined the motto, *Cure is not enough*, meaning that we are also interested in the adult the child will become and must pay attention to the long-term complications of whatever we do to children. I was privileged to chair the National Wilms' Tumour Study, part of which examined the late effects of treatment. We identified risk factors that allowed us to withhold routine treatments from low risk patients, and to intensify treatments for those at most risk.

From the same study came the use of cooperative trials techniques to answer social questions: What are the costs associated with treatment A versus treatment B? Can treatments be simplified and completed in 10 weeks rather than 15 months, or given once rather than for 5 days running? These things make an enormous difference to society as well as to children and their families.

What can paediatric oncology teach the wider field?

To adopt the clinical trials mechanism more widely. About 10% of adult cancer patients are entered into trials, compared with 80% of children in the US. For this we are indebted to the courage of parents who have allowed their children's treatment to be decided by a figurative flip of a coin. Adults with cancer have not had the same access to this mechanism for answering questions and progress has not been so rapid. Though that is also because paediatric cancers are amenable to drugs that were discovered earlier, 50–60 years ago, while adult cancers are not so responsive.

Paediatric oncologists tend to recognise their own limitations and cooperate. The 'ultimate authority' attitude is more prevalent among those treating adult cancers.

Where does the future of paediatric oncology lie?

The answers to many questions lie at the molecular level. The childhood cancer neuroblastoma, for example, can disappear spontaneously, remain as a non-threatening lump or progress aggressively. Laboratory scientists are studying the pathways and signals involved and coming closer to understanding these mechanisms. This cancer will lead the way in the molecular approach to diagnosis and management of cancer.

Childhood cancers offer unique insights into molecular biology and genetics because other factors aren't involved. The cell itself contains the clues to its origins. Neuroblastoma is the prototype and I predict that within 10 years or so, we'll understand its development and know which children will recover. It will be possible to interfere at the molecular level so that tumours can remain as benign lumps if not made to disappear entirely.

And for yourself?

For the immediate future, my project is to work with those who promise to restore my 'America the Beautiful', now so transformed.