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Drugs approval "still too slow"

Moves by the European Commission to speed up the drugs approval procedure will come too late for many patients, says a UK expert. Professor Gordon McVie, director-general of Cancer Research Campaign says the situation is "simply not acceptable".

The European Medicines Evaluation Agency (EMEA) stated in April 2001 that European patients usually have access to new drugs within a year. However, according to Professor McVie (*Ann Oncol* 2001, **12**, 1033–1035), this claim does not hold true for some cancer drugs. It took 18 months to approve Herceptin, while in the States, the Food and Drug Administration (FDA) approved the same drug within 4.5 months. Overall, EMEA has taken on average 489.5 days to approve cancer drugs over the past year, he says.

Other types of drug such as anti-retrovirals appear to have benefited from the close relationship between a patient organisation—the European AIDS Treatment Group (EATG)—and the EMEA. Approval of anti-retrovirals in Europe is now sometimes faster than in the US. By contrast, European cancer patients have never met with the EMEA, he says.

Drugs for cancer, along with central nervous system and haematological drugs also have a particularly high rate of negative outcomes. "Of great concern is that 13 (38%) of the applications with a negative outcome through the centralised procedure had been authorised by the FDA. The greatest discrepancy between the two agencies was for cancer drugs," says Professor McVie.

Professor McVie accuses EMEA of taking a risk aversion rather than a risk management approach to the approval of drugs for cancer. "In the case of a life threatening disease with few therapeutic options and where many patients are more than willing to take risks, this is an inequitable and unsupportable position," he says. It would be more logical and just to determine patients' willingness to share some of the risks associated with drug approval if it meant drugs would be approved sooner.

A further problem is that the EMEA does not generally accept effects on surrogate endpoints as evidence for the approval of cancer drugs. Agents derived from biotechnology have different mechanisms of action to cytotoxic drugs and traditional criteria for evaluating responses in phase I and II are becoming less applicable. "It is unacceptable that EMEA has not given due consideration to this issue," he says.

However, in July 2001, the European Commission announced a proposal to review EU pharmaceutical legislation. Mr Erkki Liikanen, member of the European Commission and responsible for Enterprise and the Information Society said there would be no major changes to the fundamental principles of EMEA, but that the positive aspects would be reinforced. "We want to increase the availability of new and innovative medicines on the European market. . .. This will also ensure that EU scientific assessments for major new medicines are as fast, if not faster than those performed by the US FDA."

To this end:

- A fast-track registration procedure will give products of 'significant therapeutic interest' top priority,
- Conditional marketing authorisation to meet specific and identified patient need will allow authorisation on the basis of sufficient but not definitive scientific data, and
- A European-wide system for 'compassionate use' of drugs before authorisation will prevent discrimination on the grounds of location.

Fluid intake "not related to bladder cancer"

Risk of bladder cancer was not clearly linked to total fluid intake in a study by French researchers. Drinking coffee increased the risk for men, but no association was found among women (*Int J Cancer* 2001 **93**, 880–887).

The study included 765 people with bladder cancer in several French hospitals between 1984 and 1987. They were matched with 765 controls admitted to the same hospital for reasons other than cancer. A limitation of the study was that information on fluid intake was obtained retrospectively, after the diagnosis of cancer.

There was a positive but not significant association between the intake of tap water, including that in coffee and tea, and of bladder cancer risk in men. One suggestion is that organochlorine products produced by chlorine treatment of water may be carcinogenic. "A more detailed analysis . . . is underway and will enable a more precise identification of the effects related to the organochlorines in drinking water," the researchers say.

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Most siblings "are not at increased risk"

Brothers and sisters of a child with a common cancer are not at increased risk themselves, say Nordic researchers (*Lancet* 2001 **358**, 711–717). They found that, apart from known rare cancer syndromes, such as Li–Fraumeni, paediatric cancer is not itself an indicator of increased cancer risk in siblings. This means there are unlikely to be recessive genetic conditions which play an important role in cancer development, they say.

The study covered Denmark, Finland, Sweden, Norway and Iceland; and included 42 277 siblings of 25 605 children with cancer. Data was obtained from cancer and population registries and included virtually everyone diagnosed with cancer as a child or adolescent from the 1940s and 1950s onwards.

Overall, siblings had 2 to 3 times the population's risk of cancer in the first decade of life. However, when the 56 families with well-described familial cancer syndromes were excluded from analysis, cancer risk in siblings was equivalent to that in the general population.

Further, relatives of a child with one of the syndromes were only at increased risk when they were at the age of the child at diagnosis. Any increase in risk disappeared altogether once they were 30 years old.

The study found no link between childhood and adult cancers, suggesting that shared environmental exposures in childhood have little effect on subsequent cancer risk in Nordic countries. However, the researchers themselves point out that the maximum follow-up in the study was 40 years. "We need additional follow-up and molecular epidemiological studies to assess the possible interplay between environmental factors and genetic susceptibility in cancer causation, especially for cancers occurring later in life," they conclude.

Commenting on the study, Dr Anneke Lucassen (Southampton University, UK) said the work overturns previous suggestions that unidentified genes may put siblings are at increased risk. "This study suggests there are unlikely to be any undiscovered genes that are significant causes of childhood cancer," she said.

Placenta gives clues to breast cancer risk

Markers of reduced placental size or function can predict substantial reductions in women's subsequent risk of breast cancer, US researchers say (*JNCI* 2001 **93**, 1133–1140). In combination, factors such as a small placenta or increase in blood pressure were associated with up to a 94% reduction in breast cancer rate.

Women who have pre-eclampsia during pregnancy are known to have reduced risk of breast cancer later. Following this, the researchers found that smaller placentas, maternal floor infarction of the placenta and a large increase in blood pressure between second and third trimesters were independently associated with reduced breast cancer rates.

The study included 3804 San Franciscan women who gave birth between June 1959 and September 1966. They were a subset of the Child Health and Development Studies, a cohort that has been followed for 40 years. The women were interviewed while pregnant and clinical measurements during antenatal visits, labour and delivery were recorded.

Women aged 30 at their first pregnancy, who had all risk factors–low placental weight, smaller placental diameter, large blood pressure increase, and maternal floor infarction of the placenta—had a 94% reduction in subsequent breast cancer risk. Possible explanations include reduced production of oestrogen by a smaller placenta; or antagonism of oestrogen by rising androgen levels in the last weeks of pregnancy: androgen levels are greater among women with pre-eclampsia.

Whatever the reason, this reduction in breast cancer rate is among the largest ever reported. "We believe that these findings warrant investigation of biologic factors that may explain these observations. This line of investigation could lead to prevention and treatment strategies for all women," the researchers say.

Patients want more information

Doctors' provision of information was the most frequently criticised aspect of care in survey of patients at the European Institute of Oncology (EIO), Milan. One in 5 patients wanted more information on their illness, tests and resources for help (*Oncology* 2001 **61**, 120–128).

Patients completed the EORTC's QLQ-C30 before discharge and the Comprehensive Assessment of Satisfaction with Care (CASC) once they were home. The study included 133 consecutive patients at EIO and aimed to evaluate the feasibility of conducting such a survey.

Only 7% of the patients criticised the availability of nurses, and 5% or 7% nurses' or doctors' human qualities, respectively. More than 19% were dissatisfied with the provision of information.

Patients' satisfaction was more strongly related to their quality of life than to objective factors such as disease stage. Higher satisfaction was related to longer hospital stay, which is surprising since most patients prefer to be at home. However, the patients questioned had no specific care co-ordinator responsible for providing information and assuring continuity of care. The researchers say, "The implication of this result is the necessity of enhancing patients' information and education regarding medical and nursing care at home before discharge."

Breast cancer and Friedreich's ataxia

A link between breast cancer and Friedreich's ataxia (FRDA) has been suggested. Scottish doctors report the case of two sisters who had breast cancer aged 39 and 42 years and who both developed a late onset form of FRDA in their 30s (*Eur J Surg Oncol* 2001 **27**, 512–514).

A literature search revealed little evidence supporting an association between malignancy and FRDA and the researchers say it could be a coincidence. However, they stress that the diagnosis of ataxia telangectasia (AT) must be considered in any patient with ataxia and cancer as it alters management. These patients have an increased sensitivity to radiation and are at increased risk of a second tumour.

Chemoradiotherapy for cervical cancer

A Cochrane review has confirmed that concomitant chemotherapy and radiotherapy improves survival in cervical cancer. A systematic review of all randomised controlled trials carried out between 1981 and 2000 found a potential survival benefit of 12% compared with radiotherapy alone (*Lancet* 2001 **358**, 781–786).

In February 1999, the US National Cancer Institute issued an alert that chemoradiation should be considered for all patients with cervical cancer. However, the published trials differed in the treatments used, the patient population and formed only a subset of all trials for chemoradiotherapy for cervical cancer.

The Cochrane review included 4580 randomised patients included in 17 published and two unpublished studies. The authors say the review is the most comprehensive and reliable summary so far of the effects of chemoradiotherapy. In addition to the overall survival benefit, they found a 16% benefit in progression-free survival and significant benefits on both local and distant recurrence.

They conclude that the evidence favours chemoradiotherapy and say further, "Because our results are derived from trials of different populations, with different treatment regimens and supportive care facilities, they are potentially generalisable".

Zometa: applications filed

Novartis filed applications for zoletronic acid (Zometa) with health authorities at the European Agency for the Evaluation of Medical Products (EMEA) and the Food and Drug Administration (FDA) in the US, in September 2001.

The company is seeking marketing authorisation for use of the biphosphonate in the treatment of bone metastases associated with a broad range of tumours, including prostate, breast, lung and multiple myeloma.

MBL infusions ''could reduce infections''

Infusions of mannose-binding lectin, a circulating serum protein, could in future reduce the risk of infection among people undergoing chemotherapy, suggest UK and Danish researchers. Two separate studies (*Lancet* 2001 **358**, 614–618; *Lancet* 2001 **358**, 637–638) demonstrated the link between deficiency of MBL and severity of infection.

MBL deficiency is known to be caused by point mutations of the *MBL* gene which are found in up to a third of the population. The London-based researchers followed 100 children receiving chemotherapy and found that those with *MBL* mutations had twice as many days of febrile neutropenia as those with the wild-type over a period of 6 months. The *MBL* genotypes in their study group were virtually identical to those in the general population.

MBL levels among the children with the wild-type were higher than those in healthy individuals, and levels increased further during a febrile episode. However, those with MBL deficiency showed no significant rise in concentration during febrile episodes.

Determination of the MBL status of all children receiving chemotherapy for cancer would help identify those at risk of excess infections and permit use of appropriate measures, they say. Further: "Plasma-derived human MBL has already been successfully given to a patient with frequent infections and we suggest that a formal trial of efficacy in cancer patients is now indicated."

The Danish group investigated adult patients with leukaemia. They found a link between low concentrations of MBL before chemotherapy and serious infections afterwards. In their population, even biologically normal MBL concentrations were associated with increased risk of infection. "Our findings suggest that patients with low MBL concentrations could benefit from replacement therapy with MBL before and during chemotherapy," they say.

An editorial (*Lancet* 2001 **358**, 598–599) agrees. It calls for larger studies and further analysis, and concludes: ''In the longer term, replacement therapy is a tantalising possibility.''

BRCA mutations ''relatively rare in Sweden''

Almost half of the young women diagnosed with breast cancer had relevant family history but few had *BRCA1* or *BRCA2* mutations, a Swedish study found. Only 9% of women with early-onset breast cancer had a germline mutation in one of the genes. The researchers suggest that other genetic factors are at play (*JNCI* 2001 **93**, 215–223).

All women under 41 years who were diagnosed with breast cancer in southern Sweden between 1990 and 1995 were included. Family history was established and *BRCA* status determined for 89% of the women.

Young women, those with at least one first or second degree relative with breast or ovarian cancer, and women with bilateral breast cancer were most likely to carry *BRCA* mutations. But even among women with a strong family history of breast and ovarian cancer, only 39% had *BRCA* mutations. ''Some remaining families could carry mutations in other susceptibility genes, such as *TP53*, *CHK2* and *p16*, known to be associated with early-onset breast cancer'' the authors say.

An accompanying editorial (*JNCI* 2001 **93**, 1188–1189) points out that though population-based studies provide unbiased estimates of prevalence and are important scientifically, they have little relevance in the clinic. Patients seeing genetic counsellors tend to have a much higher risk. The author, Dr Donald Berry (University of Texas MD Anderson Cancer Center, USA) states that a consecutive series of women in a clinic found 85% had *BRCA* mutations.

"A larger question ... is whether knowing one's risk of harbouring a mutation matters to a woman," he said. A woman diagnosed with breast cancer might choose bilateral mastectomy and oopherectomy if she has an 85% chance of carrying a mutation. "Providing an accurate assessment of genetic risk can be important to patients," he said.

AWARDS AND APPOINTMENTS

Prize for toxicologist

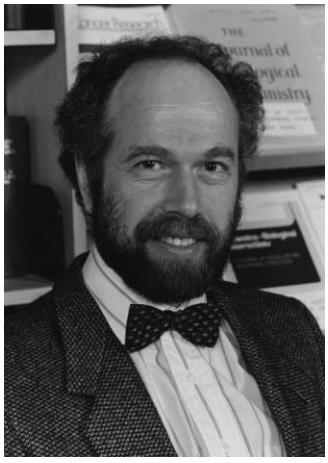
Professor Roland Wolf (Ninewells Hospital, Dundee, Scotland) has been awarded the Zbingen Prize for his outstanding research contribution to the science of drug or chemical toxicology.

The prize was awarded at the annual Eurotox Congress in Istanbul, Turkey in September 2001, and Professor Wolf gave the Gerhard Zbiden Memorial Lecture. He outlined the development of new methodologies to understand how toxic chemicals may cause disease and the factors which determine the effectiveness of therapeutic drugs. He discussed how an individual's genetic background may determine the outcome of drug therapy and how, in future, 'personalised' drugs will be prescribed on an individual basis.

Professor Wolf, who is now honorary director of Imperial Cancer Research Fund (ICRF)'s Molecular Pharmacology Unit in Dundee, took his BSc in Chemistry and PhD in Biochemistry at University of Surrey in Guildford. He has worked at the National Institute of Environmental Health Sciences in North Carolina, the Institute of Toxicology in Mainz, West Germany, and as a visiting scientist for Zeneca, UK. He was head of the ICRF's research laboratories in Edinburgh, UK and later head of molecular pharmacology there, before moving to Dundee in 1992.

The main focus of his research is to understand the pathways which determine the sensitivity of cells to drugs, environmental agents and chemical toxins. His team's molecular and genetic studies aim to increase understanding of how chemical agents interact with cells, how this influences their therapeutic and toxicological properties and how genetic polymorphisms relate to disease susceptibility, adverse drug pharmacology and toxicology.

In the late 1980s, he and Nigel Spurr investigated the lack of activity in cytochrome p450 cyp2d6/debrisoquine hydroxylase. Their work resulted in the discovery of the major gene-inactivating mutation responsible for this defect and allowed the development of DNA-based tests to identify people at risk of adverse drug reactions. It also led to investigation of the relationship between this polymorphism and disease susceptibility. More recently, he has been involved in the development of new tests for novel pharmacogenetic polymorphisms.



Professor Roland Wolf

Professor Wolf is a member of numerous national and international panels, a Fellow of the Royal Society of Edinburgh and of the Academy of Medical Sciences.

New endpoints

New statistical methods will speed up the assessment of potential drugs, according to Xavier Paoletti, statistician at EORTC Data Center since January 2000. The Continual Reassessment Method (CRM), for example, will, he says, speed up phase I trials on new drugs.

CRM is being adapted to deal with specific situations, such as trials of an anti-angiogenesis compound. This is treatment for chronic use, and is not conventionally cytotoxic. Its evaluation in Phase I trials will use CRM and involve both imaging and marker tracking. Mr Paoletti believes that use of CRM is set to become more widespread. ''We think that the proposed metholodogy should be published to help other groups in developing early stage trials for this kind of agent. Hopefully this work will be followed by other contributions which will incorporate prospectively information from PET scans and PK studies,'' he says.

Xavier Paoletti

Mr Paoletti is also involved in a Phase II ECSG/Brain Tumor Group trial on Glufosfamide in glioblastome multiform patients. The EORTC's New Drug Development Unit has developed a framework for screening anti-cancer agents for high-grade gliomas, which aims to specify new criteria for early evaluation of a drug's activity. ''The use of marker segregation is a promising way to better identify a population of potential responders,'' he says.

He is enjoying the innovative approach at the EORTC to designing and implementing studies: "At the Data Center, there is an excellent and fruitful interaction between medical advisors and statisticians".

Samantha Christey
EORTC Communications Officer

INTERVIEW

Professor Herbie Newell is Professor of Cancer Therapeutics at University of Newcastle, UK. He chairs the EORTC Laboratory Research Division and is a member of the EORTC New Treatments Committee. He is the pre-clinical chair of the UK Cancer Research Campaign (CRC)'s Phase I/II Committee and chairs the CRC New Agents Committee.

Professor Herbie Newell

Where did you train?
I left school at 16 and became a laboratory technician, first at the Marie Curie Memorial Foundation and then at the Institute of Cancer Research (ICR), London. I took a pharmacology degree part-time, and my PhD on the pharmacology of anti-cancer drugs was from the University of London.

Who inspired you?
Many colleagues over the years, but in particular Professor Tom Connors in London. He emphasised selectivity in cancer pharmacology; developing ways to damage the tumour and spare the patient are paramount. Also—he taught that science should always be fun.

Why did you choose to work in the field of cancer?
I was interested in science at school and saw that a job was going at the Marie Curie Memorial Foundation. I have no regrets!

Did any other branch appeal?
Not really, I was always struck by the fact that small, often very simple, molecules can have such a profound and beneficial effect on complex diseases like cancer in complicated organisms like humans. It never ceases to amaze me that someone with an illness that is almost certainly going to kill them, can cured with simple drugs. Of course, this is still in a minority of patients.

Might you have done something else altogether?
Until my academic responsibilities increased, I was active in the Green movement and stood for Parliament as a member of the Green party. I am increasingly concerned about the stability and sustainability of our environmental, economic and political systems.

What has been the highlight of your career to date?
I guess my most clinically useful contribution to cancer was in the development of carboplatin. Hilary Calvert and I were working in Ken Harrap's department at the Institute of Cancer Research (ICR, London) and we showed that understanding the pharmacology of a drug allows you to tailor therapy for each individual patient. Carboplatin is cleared by renal excretion, which can be estimated prior to treatment and used to predict the dose to give each patient to get the best chance of a response, and the least risk of unacceptable toxicity.

. . . and your greatest regret?
My greatest frustration is that we don't have more new medicines to offer cancer patients. It is taking longer than I would like to convert insights into the biology of cancer into effective new treatments. There are hopeful signs, but for the vast majority of cancer patients radio- and conventional chemotherapies, with all the associated side effects and limited activity, is still their best hope.

If you could complete only one more task before you retire, what would it be?
To devise better ways of finding out whether drugs are hitting their targets in patients. We still too often give a drug and then stand back and observe what happens in terms of clinical efficacy and side effects. Taking a biopsy gives limited information and can be distressing for the patient. Non-invasive techniques are beginning to come on-line, but there is still a long way to go.

What is your greatest fear?
Scientifically, that the genetic instability of tumours will mean that resistance develops quickly to the new generation of drugs selectively targeted against molecular pathways of disease. If tumours are able to develop resistance by throwing-up gene mutations, deletions and translocations, and as a result survive treatment, the next generation of drugs may not be the answer to all our prayers.
Politically and environmentally, I'm afraid that we have got it wrong big time and that it is already too late. We need to create a world order based on justice and peaceful cohabitation, which does not involve the destruction of the planet.

What impact has the Internet had on your working life?
Huge, for correspondence and for rapid access to sources of information.

How do you relax?
Rock climbing, mountain walking, cycling, and the occasional pint of beer!

Who is your favourite author?
The most inspirational book I have ever read is Nelson Mandela's *Long Walk to Freedom*. It is incredible how the man maintained his sense of justice and resisted bitterness through so many years of incarceration.

What do you wish you had known before you embarked on your career?
That the administration and management involved in science can become all-consuming. I should have savoured my years in the lab more than I did! I would like to see a career structure for scientists which recognises this, and allows them to continue hands-on laboratory research.

What piece of advice would you give someone starting out now?
Enjoy your work and be adventurous! Try different things, work in different places, use different techniques and even work in different areas of science.

What is your greatest vice?
According to my wife, my children and some of my colleagues I can be irritatingly jolly—if you call that a vice!