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'Need for improvements' in drug development

Improvements in the drug development process 'are clearly necessary,' according to Dr Richard L Schilsky (University of Chicago, Illinois, USA). He said such improvements are needed 'to speed drugs to market that are proven to be safe and effective at the time when they arrive in the pharmacy or soon thereafter' (*JCO 2003 21: 20 3718–3720*).

The US' Food and Drug Administration (FDA) has approved 16 cancer drugs, including irinotecan, docetaxel and capecitabine using the accelerated approval process, Dr Schilsky says. The drugs had an effect on a surrogate endpoint that was reasonably likely to predict clinical benefit. Postmarketing studies are then required to establish clinical benefit with certainty, and these 3 drugs went on to obtain full approval on the basis of randomised controlled trials.

"SPONSORS AND THE FDA MUST WORK TOGETHER TO IMPROVE THE PROCESS"

Accelerated approval has "generally been considered an effective mechanism," but it assumes that tumour response is a reasonable surrogate, that sufficient safety data exist at the time of accelerated approval, and that postmarketing studies will be completed.

Dr Schilsky writes that response rate "is reasonably likely to predict clinical benefit, at least for certain diseases and certain drugs," but doubts whether there is sufficient data available at the time of accelerated approval to ensure that new agents are safe. The approval is often based on phase II studies involving small numbers of patients, which may not allow recognition of uncommon toxicities, rare drug interactions and unusual pharmacogenetic syndromes for example.

Furthermore, postmarketing studies are taking longer than expected, partly because "patients and doctors have been willing to accept that a commercially available product is proven to be safe and effective even when the definitive studies to support this conclusion have not been completed". There is little incentive to enrol in trials when a drug is both available and reimbursed.

Dr Schilsky points out that the FDA has never withdrawn a cancer drug where clinical benefit could not be confirmed "which leads to concerns that drugs of unproven benefit may remain on the market for prolonged periods of time."

He suggests that confirmatory trials should be ongoing at the time when accelerated approval is granted. "The FDA has not proposed that accelerated approval could be based on a planned interim analysis of a definitive randomised trial." It would mean that approval could be applied to less refractory patient populations, would give greater confidence that the new agent is producing the observed effect and may permit other endpoints to be used as a basis for approval.

"WHY ENROL IN A TRIAL OF AN AVAILABLE, REIMBURSED DRUG?"

Sponsors and the FDA must work together to improve the process of oncology drug development, Dr Schilsky says. "As currently used, accelerated approval provides a mechanism for more rapid drug approval but may, in fact, reduce the opportunity to prove that new drugs are truly safe and effective."

Positive opinion for Fulvestrant

The Committee for Proprietary Medicinal Products (CPMP) has recommended approval of fulvestrant (Faslodex) "for the treatment of postmenopausal women with oestrogen receptor-positive, locally advanced or metastatic breast cancer for disease relapse on or after adjuvant anti-oestrogen therapy, or disease progression on therapy with an anti-oestrogen."

The CPMP, the scientific advisory body to the European Commission, concluded that on the basis of data submitted, there is a favourable risk balance for fulvestrant and recommended the granting of marketing authorisation.

Fulvestrant is an oestrogen receptor antagonist with no agonist effects. It down regulates the oestrogen receptor. Professor Tony Howell (Christie Hospital, Manchester, UK) says it "offers an additional treatment option with a different mechanism of action to any other currently available endocrine therapy."

The final decision will be taken by the European Agency for the Evaluation of Medicinal Products (EMEA) and, if accepted, would result in a single licence throughout the EU, Norway and Iceland, plus additional countries with the number of EU member states expands in May 2004. It is the first time manufacturer AstraZeneca has submitted a Marketing Authorisation Application) via the European Centralised Procedure.

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New gene for breast cancer

A new gene for breast and ovarian cancer may provide the missing link between hereditary breast cancers and sporadic, non-inherited forms. The gene, called EMSY, was discovered by a consortium of Cancer Research UK scientists and doctors (*Cell 2003 115:5*).

Inheriting faulty BRCA genes can trigger hereditary breast and ovarian cancer, but no role had been established for these genes in sporadic tumours. The Cancer Research UK team now suggest that EMSY shuts down the action of functional BRCA2 to fuel the development of cancer.

A team at the Wellcome Trust/Cancer Research UK Institute (University of Cambridge, UK) searched for sequences of DNA that interact with BRCA2. They described and isolated the gene EMSY, which plays a role in turning genes on and off and in repairing damaged DNA. It was highly effective at switching off BRCA2.

The gene was called EMSY after cancer nurse Emma Hughes-Davies, the sister of Dr Luke Hughes-Davies, who discovered the gene.

The Cambridge scientists found extra copies of EMSY in the first few tumour samples they tested. Then, working with a team from the British Columbia Cancer Agency in Canada, they analysed the gene in 551 breast and 360 ovarian tumours. Extra copies of the gene were found in 13% of breast cancers and 17% of ovarian cancers, but never in normal tissue and rarely in other tumours.

Professor Tony Kouzarides (University of Cambridge, UK), said, "Discovering such an important new gene is very exciting and gives us the piece in the jigsaw we've been looking for. It's taken us 6 years to get here, but it's been well worth the effort".

"We'll now have a much more sophisticated image of the genetic changes triggering breast and ovarian cancer in women who haven't inherited a high risk of cancer, but develop it anyway. It's going to give us new lines of investigation and potentially exciting angles of attack."

EMSY appears to play a particularly important role in aggressive forms of breast cancer. Women whose tumours had extra copies of the EMSY gene survived for 6.4 years on average, compared with 14 years for those whose breast cancers had normal amounts of EMSY. The difference in survival was greatest among women who at diagnosis had not suffered any spread of the cancer to their lymph nodes. This suggests it might be possible to test for EMSY early on, to predict how aggressive the disease is likely to become.

Professor Robert Souhami, Cancer Research UK's Director of Clinical and External Affairs, said, "Discoveries like this don't come along very often and it's taken a major collaborative effort. The gene will hopefully bring significant advances in treating female cancer patients."

'Rigorous criteria' needed in microarray studies

The clinical use of DNA microarrays must be "rigorously evaluated," researchers say (*The Lancet 2003* ***362****: 1439–44).* Attention must be paid to potential pitfalls: "DNA microarray studies incorporating patients' samples are clinical studies and should not be spared the rigorous criteria imposed on clinical research," they concluded.

Working in Greece and the US, the researchers systematically analysed Medline reports on the use of the technologies in microarray studies addressing clinical issues on cancer outcomes and correlates predicting cancer outcomes and correlates. They identified 84 reports published between 1995 and April 2003.

The predictive performance of the technique was variable. "In many cases molecular classifications were not subjected to appropriate validation," they said. Only 26% of the studies attempted independent validation or cross-validation of proposed findings. "Incomplete cross-validation can lead to inflated estimates of accuracy," they said.

Small sample size is another problem with a median of 25 (15–45) patients included in the studies. This, again, can lead to "over-promising" results. Furthermore, publication bias could affect negative studies disproportionately, meaning that "validation performance may be worse than reported."

Significant associations were 9.7 times more likely per ten-fold increase in microarray probes. "Unless there is a specific rationale to limit the number of explored genes, use of comprehensive microarrays with a larger number of gene probes maximise the yield of information," they write.

Before a molecular marker can be accepted into routine clinical practice, they say, it should be supported by studies with "sufficiently large sample sizes, prestated hypotheses, adjustment for other classic prognostic factors and therapies used, proof of reproducibility, widely available quality control systems, clear interpretation in clinical practice, and independent validation across several. . . studies."

DNA microarrays may have wide-ranging applications but "complete uncensored reporting, publicly available data, and standardisation within and between institutions are essential," they conclude.

The researchers call for the formation of repositories and registries, where any research institution could deposit raw or processed data, to allow comparison of independent works on the same malignant order.

An editorial (*The Lancet 2003* ***362****: 1428)* stressed further the need for standardisation. "The authors were faced with the challenge of attempting to determine what exactly was done in each of the publications they examined." The author, Dr Neil Winegarden (Max Bell Research Centre, Toronto, Canada) said that groups such as the Microarray Gene Expression Data Society (MGED) are working to provide a framework for common data formats. "It is important that journals and authors begin to follow these guidelines because they facilitate understanding of the approach taken and enable reproduction of the data."

Dr Winegarden also points to the need for further technology development. "Array providers need to lower the cost of arrays while increasing content," he says.

EUROFILE

Improved health for all in the new Europe?

Will the enlargement of the European Union bring about improved health for all, simply magnify existing differences, or lead to a diminution of healthcare standards all round? Policymakers have been struggling with the question for months now, and there is still no obvious answer. The arrival of 10 new countries in the EU in the summer (2004) will bring another 170 million people into the fold, and exacerbate the health gap that already exists between European countries.

It will also increase the pressure for patients to be treated in other countries. This is becoming a pressing issue for national healthcare systems in the light of recent European Court of Justice (ECJ) judgements and increasing migration of labour from southern European countries to those further north.

EU Regulation 1408/71 is designed to co-ordinate social security systems. It allows patients to receive treatment in other countries using the E106 (migrant workers), E111 (temporary stay) and E112 (pre-authorised care) form. The latter demands that any treatment in another country, if it is to be reimbursed, must first be approved by the health authorities of the country of residence. But in a number of ECJ judgements, the Court ruled that restriction of consumer choice across borders—i.e. refusing to allow people to decide where they receive healthcare—fell foul of the EU's stated aim of allowing free movement of services.

So is this a good opportunity for accession countries to make money to plough back into their under funded health services? Well, yes and no. The new EU member states will certainly be in a position to provide healthcare services much more cheaply than existing members. But the arrangements for reimbursement are still unclear, and new states could overload their health facilities with foreign patients, only to find later that they are not paid for the work. Providing services only to those who are paying for themselves would severely restrict the market.

Accreditation also creates problems; common accreditation procedures are still under discussion. Patients from other countries will need to be assured that the treatment on offer is at least as good as that at home.

The mobility of healthcare workers after European enlargement is another difficult issue. Legislation allows free movement of health professionals and mutual recognition of their qualifications. Physicians and nurses from the new states may be tempted to work where salaries are higher and, given the shortages of healthcare workers in many current member states, additional staff with accepted qualifications will be a great help.

"PROFESSIONALS MAY MOVE FOR HIGHER SALARIES"

But this potential brain drain of healthcare workers poses a serious problem to the already overstretched health services of the accession countries. A harmonious co-existence of healthcare resources and systems is desirable, but it is not clear how to achieve this. The declaration issued after the 2003 European Health Forum, Gastein, stated that it depends on ensuring an adequate supply of health professionals throughout Europe "through planning and ethical recruitment, accessibility to innovative medicines across Europe, and sensible patient flows". The Health Forum President, Dr Gunther Leiner, said "European added value is in the gathering of information, monitoring of progress, providing training and networking opportunities, addressing macroeconomic issues and supporting initiatives between member states."

Before this added value can be achieved, there are many problems to tackle. Accession country health ministers have recognised this, and set up a steering group to co-operate more closely. On 21 September 2003, the health ministers of Cyprus, the Czech Republic, Hungary, Lithuania, Malta, Poland, the Slovak Republic and Slovenia signed the "Prague Declaration" in which they committed themselves to:

- fully endorsing the conditions for mutual recognition of the qualifications of health workers and ensuring the free movement of persons and services. Introducing a registration system for healthcare workers;
- improving the coordination of organs available for transplantation by connecting transplant centres to national and international databases of those in need of transplants;
- intensifying national efforts to implement health promotion policies and prevention programmes against smoking, alcohol and drug abuse;
- expediting the implementation of national legislation in order to avoid any major conflict with EU law at the time of accession;
- recommending that EU finances are set aside for special healthcare programmes to discourage patients from shopping around for healthcare treatment as this puts an extra burden on national health resources;
- establishing a Steering Group of health ministers with a rotating presidency, to be held by the Czech Republic until the end of 2004.

Enlargement remains a big challenge for healthcare systems, but the opportunities for improved health are huge, too. It will take some time, and no doubt many tonnes of academic research papers, before we really know the outcome.

Mary Rice
Brussels

Pakistan: Unique risk factors for breast cancer?

The protective effect of hormones on breast cancer risk, well-documented in Western literature, is not seen among Pakistani women, a conference heard. Mr Saif-ur-Rahman (Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore, Pakistan) said that risk factors for breast cancer in Pakistani women seem to differ from those commonly seen in the West.

He presented data from a series of 1040 cases diagnosed between August 1996 and July 1999 at Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH & RC). Neither normal/late menarche (median age 14 years), early menopause (median age 45 years) nor parity had any protective effect against breast cancer. Median age of first full term pregnancy was 20 years and 852 patients (81%) did not use contraceptive pills for any appreciable period of time. Mr Saif-ur-Rahman said this meant that hormonal factors do not appear to exert their protective effect over Pakistani women.

He was speaking at the 6th Shaukat Khanum Memorial Cancer Symposium (October 4-5, 2003, Dubai, UAE), which was held in the UAE to enhance regional cooperation in the fight against cancer. Sessions covered breast, paediatric, haematological, and urogential cancers; and presentations came from institutions in Pakistan, the UK, Cameroon, and Saudi Arabia, among others.

Most worrisome, according to Mr. Saif-ur-Rahman, was the fact that advanced stage presentation was common, with 478 (45%) cases presenting with stage III and IV cancer, in sharp contrast to western literature. This underlines the need for mass education, and breast screening programs. Moreover, a comprehensive tumour registry system in Pakistan would help uncover other risk factors that may be unique to our female population, he said.

Dr Zeba Aziz, (Allama Iqbal Medical College, Lahore, Pakistan) presented the role of socioeconomic class on breast cancer in Pakistan. Between April 1997 and May 2002, 286 patients were recruited from three economic strata: high, medium, and low. Significant differences were noted in patients belonging to different social strata. 5-year disease free and overall survival were 86% and 74% for the high income group, 48% and 68% for middle income group and 31% and 49% for low income group.

Pakistan is a country of 140 million people with an estimated 200,000 new cases of cancer annually. It has the highest incidence of breast cancer in the whole of Asia bar Israel. Prior to the establishment of SKMCH & RC, no comprehensive facility dedicated to the diagnosis and treatment of cancer existed in Pakistan. SKMCH & RC was established to provide the best possible treatment of cancer to all patients, irrespective of their ability to pay. Over the last 8.5 years, around 80% of all patients have been treated entirely free of cost. Funded by the donations of over 1.2 million people, the project has received widespread support both in Pakistan and overseas.

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Indian registry to study hereditary cancers

Mathematical models used by developed countries to predict cancer risk have limited applicability in India because of differences in disease incidence. In a move to eliminate this problem, India has established the Population-based Hereditary Cancer Registry at the Cancer Institute in Chennai. Despite 14 other population-based registries in the country, this registry will collate, for the first time, data on the incidence of hereditary cancers.

The new registry covers the Chennai metropolitan area and data is being obtained from government hospitals and private nursing homes. Data collection is being done by trained social investigators using a questionnaire-based approach. In addition, the registry will be linked to the Madras Metropolitan Tumour Registry that records the incidence of all cancers in the city of Chennai, India.

The occurrence of hereditary cancers, such as breast and ovarian carcinoma and non-polyposis colorectal cancer have been reported before in Indian populations. However, the new registry—coupled with data from genomic sequencing—will help researchers do linkage analysis to ascertain the inter-relation between specific genes and specific cancers and hence design appropriate preventative measures for people who are carriers of mutated genes. So far, about 190 cases have been registered. "It is too early for us to talk about linkages but the mutation analysis is continuing and we hope to be able to address this issue once we complete the analysis", says Thangarajan Rajkumar (Cancer Institute, Chennai, India).

The institute has already generated some initial data about hereditary cancers. The clinic has started to offer high-risk families genetic counselling and testing for *BRCA1* and *BRCA2* (for hereditary breast and ovarian cancer); *hMSH2* and *hMLH1* (for hereditary non-polyposis colorectal cancer); and *Ret* (for multiple endocrine neoplasia types 2A and 2B, and familial medullary thyroid cancer).

The location of the registry in southern India is also an important aspect because arranged marriages between cousins is highly prevalent in this part of the country—increasing the risk of certain hereditary cancers. "The risk for hereditary cancers among an inbred population is likely to be high. One of the families with breast cancer analysed recently, was found to have a uncle–niece parentage and carried a deleterious two-base novel deletion in the *BRCA1* gene. So, it is critical to study these populations for mutations in the relevant genes", concludes Rajkumar.

Dinesh C Sharma

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PODIUM

Our moral duty to prioritise

Dr Terhi Hermanson has been Senior Medical Officer at Finland's Ministry of Social Affairs and Health since 1995. She trained in medicine at Helsinki University, where she also took a Master's degree in Social policy and Sociology. She then specialised in public health and completed a doctoral dissertation on Physicians in health care management.

Dr Terhi Hermanson

Why do we need to prioritise the healthcare on offer?
We don't have unlimited resources. Populations are ageing, people's expectations are rising, and new- sometimes effective but always expensive- technologies are being introduced. We have always had to prioritise but years ago, when there was less money, there were also fewer ways to fulfil needs.
Now, methods of setting priorities in a meaningful way are better developed and we are prepared to set priorities more openly and sensibly.

Who should set the priorities?
There are different levels. Finland was highly centralised until 1993. Now, it is de-centralised, and the State decides how much will be spent overall on health and social services, but the 450 different municipalities each have the autonomy to allocate the money within limits set by legislation. Hospitals and health centres set their own priorities and, finally, the individual healthcare provider decides what treatment to give the patient in the clinic.

We as doctors have traditionally tried to act as solicitors for the individual patient and do the best we can for each. But we cannot and should not continue like this. We have to think about the next patient to come, and about the whole patient population. If we give the very best to the first patient, there may be nothing left for those coming later.

Patients also have to be involved in decision-making more than before. They are better informed and educated and are after all, the ones most affected by the decision.

Doesn't this put doctors in a difficult position?
Yes. Doctors would like to give the very best to all patients but there is only so much money in the pot. In their private lives, doctors, like everyone else, set priorities according to financial limitations. If a parent loses their job, the family does not stop feeding one child; they decide how to feed the entire family in an adequate way on less money. It's a bit contradictory for doctors to expect unlimited funds at work. Similarly, the medical literature tends to assess the clinical value but not the cost-effectiveness of treatments.

How explicit are the priorities?
We're not planning an Oregan-style list, but we're increasingly relying on national treatment guidelines, which are drawn up by the medical profession, based on the best available evidence and constantly updated. The municipalities assess the guidelines according to the particular needs of their population, and each organisation in the area then decides how they will treat the condition, taking into account both clinical value and cost. If treatment A is 20% better than treatment B, but costs twice as much, then one might have to choose treatment B.

How do you determine the costs of treatment?
Cost assessment is best developed within pharmaceuticals, but thinking in terms of both costs and benefits should extend to all areas of health care. When companies apply for a marketing licence for new drugs to be included in the National Reimbursement Scheme, they have to present a pharmaco-economic evaluation, which includes all direct healthcare costs. A more expensive drug might be worth paying for if it reduces use of expensive hospital facilities. Companies can include indirect cost savings, such as a quicker return to work, but it is difficult to measure and many patients may be unemployed or retired.

How do healthcare professionals react?
Traditionally, doctors did not expect their decisions to be questioned, or even to be looked at by anyone else. Now they recognise that the best knowledge comes from collective experience. Guidelines are increasingly accepted. They aren't followed like cookbooks, and doctors can choose a different course of action if they can justify it.
Guidelines and health economic evaluations make priorities explicit, which is difficult, but better than setting priorities behind closed doors and hoping nobody will notice.

Is cancer a special case?
Yes, in that decisions can be life and death. Treatments can be expensive and may cure, but they can also have serious side effects. The decision about when to stop active treatment and switch to palliative care is crucial and must be carefully discussed with patients. Patients must not get the wrong impression and think their active treatment was withdrawn for financial reasons.

How will things change over the next 5–10 years?
The need to set priorities more openly and rationally will become more important. The financial limitations in healthcare will not go away no matter how rich we get and an open process is less susceptible to abuse or bias. Healthcare economics is still developing as a science, but methods are improving and it should be taught to everybody making decisions in healthcare.