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The Costs of Chemoprevention

The costs of chemoprevention of breast cancer vary dramatically according to the agent chosen, according to Professor Craig Jordan (Fox Chase Cancer Center, Philadelphia, USA). Writing in this issue of *EJC*, he estimates that the cost per case prevented can be more than 20 times higher with aromatase inhibitors, than with tamoxifen (p. 2909).

Raloxifene is more expensive than tamoxifen, but still costs less than half as much as the aromatase inhibitors, he said.

Professor Jordan was scientific chair of the STAR (Study of Tamoxifen and Raloxifene) trial, which established that raloxifene is as effective as tamoxifen in preventing breast cancer in high risk postmenopausal women. Its side effect profile was better, though: "It's a safer version of tamoxifen."

The debate must now focus on the implications for developing practical and appropriate healthcare policies on the chemoprevention of breast cancer, Professor Jordan told *EJC*: "We need to have realistic comparisons of the costs. I presented these figures at the Royal College of Surgeons in Edinburgh and the audience was flabbergasted by how expensive the aromatase inhibitors are, in real terms. They were pleasantly surprised by how much cheaper tamoxifen is."

He said he has been disappointed that, in the US at least, tamoxifen has been "killed off" in order to advance the cause of the aromatase inhibitors. "This naturally has started women worrying about uterine cancer, blood clots and so on, and throughout the 1990s there was a large amount of negative publicity. This has led to a general lack of interest in chemoprevention." However, progress has been made. In the 1990s, hormone replacement therapy was the standard of care in prevention of osteoporosis, but was associated with increases in breast cancer. Professor Jordan: "Now, half a million women are taking raloxifene to treat osteoporosis, which prevents fractures and also decreases breast cancers. It adds up to real health care savings."

Aside from the costs, cultural resistance to the idea of chemoprevention is marked in Europe and good research is needed to counter it. Professor Jordan: "We need to use the clinical trials mechanism to show that the appropriate application of agents to the right women ultimately provides benefits to the health system.

"Physicians have enough common sense to pick out the patients in whom an intervention is most appropriate. It won't suit everybody. Therapy is becoming tailored to patients and targeted, and it should be the same in chemoprevention. In thinking of a population's safety it's important to choose an agent that has advantages over more than one endpoint – such as osteoporosis and breast cancer."

FECS: The Future

FECS is to become involved in policy issues that address the pressing needs of the oncology community. A review of its role has "strengthened our resolve to look at activities that go beyond events and congresses, and that have a direct bearing on cancer policy in Europe," according to a letter from the President.

Writing to colleagues and friends, Professor John Smyth said that over the past year, FECS has been assessing in detail the role and scope of the organisation. Valuable feedback from member organisations has been taken on board.

FECS will continue to build on its world class events, and is working closely with ESMO and patient organisations "to develop an excellent programme for ECCO 14" (Barcelona, September 23-27, 2006). But in addition, increased involvement in policy issues will ensure that FECS adds value to the work of all members of the oncology community.

"We plan to focus on key areas such as educational, political and access needs, providing a forum to work with all the stakeholders involved in European oncology. Our aim is to look for synergies and to avoid duplication of effort".

"We aim to provide you with a multidisciplinary organisation embracing all those who are interested in contributing to the advancement of cancer care, research and policy across Europe".

"We look forward to your continued input and your support in our mission to make FECS a real force for good in oncology, speaking with one voice on matters that affect us all", the letter stated.

Further details of FECS' review are expected over the coming months.

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Anti-Smoking Pill Approved

The European Commission has approved varenicline (Champix), a pill to aid smoking cessation in adults. This follows approval by the US' Food and Drug Administration in May, 2006.

Manufacturer Pfizer said varenicline is a novel treatment which reduces the severity of the urge to smoke, and alleviates many withdrawal symptoms. It diminishes the sense of satisfaction associated with smoking in those who have a cigarette while on treatment, the company said. A patient support plan is available for use in conjunction with the new treatment.

In trials including 4000 smokers, 44% of those treated with varenicline had quit at the end of the 12-week treatment period. This compares with 30% of those using buproprion and 18% of those on placebo.

Posaconazole in Europe

The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMEA) has issued a positive opinion recommending approval of posaconazole (Noxafil) for the prevention of invasive fungal infections. It applies to patients receiving remission-induction chemotherapy for acute myelogenous leukaemia (AML) or myelodysplastic syndromes (MDS) expected to result in prolonged neutropenia, and haematopoietic stem cell transplant recipients undergoing high-dose immunosuppressive therapy from graft versus host disease.

CHMP also recommended approval for posaconazole for first line therapy of oropharyngeal candidiasis in patients who have severe disease or are immunocompromised, and in whom response to topical therapy is expected to be poor.

Docetaxel Available in the UK

The UK's National Institute for Health and Clinical Excellence (NICE) has approved the combination chemotherapy – docetaxel, cyclophosphamide and doxorubicin – for the adjuvant treatment of women with early node-positive breast cancer. All primary care trusts (PCTs) are expected to fund access to the treatment by the end of 2006.

Docetaxel is the only taxane currently recommended by NICE.

Social Barriers to Quality Treatment in France

Access to care in specialist centres is limited for patients living in underprivileged districts in France, say researchers. They call for special attention to be paid to the quality of care in non-specialised care centres "in order to avoid an increased social gradient in cancer mortality in France" (*EJC this issue p. 3041*).

Population-based data on the Calvados cancer registry included 5156 patients who underwent surgery for colorectal cancer between 1981 and 2000. A retrospective analysis established that living a long way from a specialist centre was an obstacle to receiving treatment there. Once this was corrected for, patients in districts where the mean income was low, or where housing is often inadequate, were still less likely to be treated in a specialist centre.

Professor Guy Launoy (University of Caen, France) said that in France, unlike some other European countries, it has not yet been established that survival rates are lower for patients treated in non-specialised centres: "It is very important to establish a difference in survival rates. In terms of public health policy, politicians would be forced to provide specialised centres if we could establish that survival is better for patients treated there. We might also be able to suggest that some hospital units, where the care provided is of insufficient quality, are closed."

The EUROCARE study found that mortality rates in France are lower than in many other European countries. Professor Launoy: "France is one of the best. But at the same time there is also more of a social gradient in mortality than elsewhere. We have some very good centres, but also important social disparities."

The social indicator used in the current study was the percentage of houses lacking a bath or shower. Professor Launoy said that future research will use deprivation scores such as Castair's index, which will allow direct comparison of results with those obtained in other countries. "It is important for the message to be clear," he said.

Relief from GI Symptoms for Patients on Opioids

A new class of peripheral opioid receptor antagonists significantly improved gastrointestinal (GI) symptoms in a phase III study presented at an International Association for the Study of Pain (IASP) meeting (Istanbul, Turkey, September 13-16, 2006). Alvimopan (Entereg), designed to treat the GI symptoms associated with opioids, significantly increased spontaneous bowel movements, according to data presented at the 5th Congress of the European Federation of IASP ® CHAPTERS (EFIC).

Opioids bind to receptors in the brain, but also to mu-opioid receptors in the gut, reducing GI motility and secretions. Adverse effects include constipation, nausea, vomiting, reflux and delayed absorption of nutrients. Unlike earlier opioid antagonists, alvimopan does not cross the blood brain barrier, and hence does not interfere with analgesia.

Study 012, presented by manufacturer GlaxoSmithKline, enrolled 518 patients with chronic non-cancer pain (who experienced less than three spontaneous bowel movements a week). It found that 72 % of patients treated with alvimopan 0.5mg twice daily met the primary end point of three or more spontaneous bowel movements a week, compared with 48 % taking placebo ($p < 0.001$). A second phase IIb study of 233 patients with chronic cancer pain, also presented, showed average weekly change from baseline for the three week treatment period was 1.9. 1.8 and 2.1 spontaneous complete bowel motions (SCBMs) for patients treated with alvimopan 0.5 mg twice daily, 1.0 mg once and twice daily respectively, compared to 1.6 SCBMs for those receiving placebo ($p < 0.05$).

Janet Fricker

EUROFILE

Battles Still Rage Over Framework 7

It is still far from clear that disagreements over the new European 7th Framework Research Programme will be settled in time for it to come into force in 2007. Although a common position was reached by a qualified majority at the Competitiveness Council in late September 2006, new battles have broken out between the Parliament and Commission, as well as within some of the Member States which make up the Council membership.

The Council's common position will now be forwarded to the Parliament for its second reading, which is expected to take place at the end of November, 2006. But regular arguments are taking place between officials from the Member States, the European Parliament and the Commission over the many amendments put forward by MEPs. The main disagreements concern the rules of participation, particularly the role of consortia co-ordinators and costing.

The Parliament wants to see co-ordinators of consortia given full legal responsibility, which would make them liable for the delivery of projects. They are asking that co-ordinators should "ensure that the legal entities.... comply with the obligations", and, in addition, that all participants in a project should be given access to intellectual property, The Commission argues that smaller partners in consortia could lose out at the hands of unscrupulous co-ordinators with full responsibility for projects, and that small/medium enterprises (SMEs), in particular, would be reluctant to join consortia if they knew they would have to share intellectual property with many other partners. On the other hand, some MEPs believe that SMEs would be more likely to apply to the Commission if co-ordinators had more power and responsibility, thus removing some of the administrative burden from the partners.

How these issues will be resolved is anybody's guess. Months of persuasion from the Commission have failed to shift MEPs, who are acting with the strong support of the Court of Auditors, responsible for independent audit of the collection and spending of EU funds and assessing the way in which the European institutions discharge their functions. A Court spokesman said; "The Parliament shares our views, rather than the Commission views, on certain things. The rules of administration deal with the administrative and financial aspects, and that is our core domain of competence." However, says the Commission, a key purpose of Framework 7 is to support high-level research that is risky and has an uncertain outcome.

"Insensitive project management is likely to reduce efficiency and effectiveness, not increase it. When we look at financial control, it is important not

''WE MUST NOT REPEAT THE MISTAKE OF OVER-REGULATION''

to lose sight of the overall objectives, which are to support research and innovation", said Dr. Monica Schofield, a member of the Sounding Board set up by Commissioner Janez Potočnik to help the Commission simplify rules for Framework 7 participants. "Much of the complexity and bureaucracy that caused so much of the frustration in Framework 6 was due to over-regulation in the rules and we must not repeat that mistake", she continued.

Parliamentarians also want to see a flat rate for projects' indirect costs specified in the rules. But many Member States and the Commission also have concerns about this, on the grounds that, at the rates proposed by the Parliament, the provision of more funds per project will be necessary and therefore fewer projects will be financed. Other countries, such as Ireland, Germany, and several new Member States support the proposal on the grounds that it would give universities some breathing space.

And once again the stem cell issue is rearing its head. The common position adopted by research ministers in September 2006 says that Framework 7 will not fund research intended to create human embryos solely for research purposes or for the purpose of harvesting cells. This means that researchers have to buy stem cells from other sources. But this is not enough for the centre-right Italian MEPs who voted against any research on human embryonic stem cells, and who are not letting the matter drop. In a letter to the Italian research Minister, the Commission president, and the Finnish Presidency, they say that they want EU funding for stem cell research to be limited to those that have been extracted before the Framework 7 regulations come into force so that "the EU's money will not be used to destroy human embryos."

There is still time to reach agreement on these issues, with the formal adoption of Framework 7 by the Competitiveness Council not due until early December 2006. Former Polish Prime Minister Jerzy Buzek, MEP, the rapporteur for the Parliament's committee on industry, research and energy (ITRE), is

''THERE IS STILL TIME TO REACH AGREEMENT''

reported to be optimistic and sees no major obstacles to reaching agreement by this date. If all goes well, first calls for proposals for FP7 projects could be published by December 2006 for submission in March 2007, and, after an evaluation period, the first FP7 project could begin at the end of 2007 or early 2008.

But others see that some of the differences between the Parliament, Council, and Commission are major and that the chances of reaching a deal in time are limited. With Framework 6 running out at the end of 2006, a speedy solution to the disagreements must be found if European research is not to suffer further.

Mary Rice
Brussels

Speeding up cancer-drug development

The results of three phase II trials assessing the effectiveness of sorafenib (a multikinase inhibitor) in advanced myeloma, metastatic renal-cell carcinoma, and advanced hepatocellular carcinoma were published between June and September, 2006. Phase III testing of the drug is also in progress in patients with non-small-cell lung cancer. This kind of simultaneous testing for different indications aims to shorten drug-development times: the days when cancer drugs were tested for one indication after another are nearing an end.

The rapid progression of safe and effective drugs from the laboratory to the bedside is in everyone's interest. For patients, slow drug development could mean dying before taking a promising drug. For pharmaceutical companies, every day of development saved could be worth US$1–3 million in sales. But are simultaneous trials the answer?

Such trials are rational if the drug's mechanism is understood. "Targets for many developing drugs are now known", says Karol Sikora (Buckingham University, UK), "so understanding the molecular abnormalities associated with response means that the type of primary tumour is less relevant".

"This approach reflects a combination of confidence by the drug company in its investment, based on the science of the drug and phase I trials", says Thomas Jones (Clinical Research Associates, Basle, Switzerland). "Simultaneous trials bring the drug to the licensing process with more data and for more indications, saving 3–4 years of waiting for patients, and preventing lost sales for each valid indication not tested."

''IF THE DRUGS WORK, SOCIETY WILL PAY''

However, the costs of this approach are enormous and only large companies with careful phase-transition review processes and adequate financial resources can attempt it. Should the product fail, even in one area, the losses could be huge for drug companies and patients. "Drug companies benefit by having more indications—a larger market—for a drug at the time of registration", states Jones. "But if a drug has too many potential indications after phase II, the danger is that the company will choose the wrong indication for phase III development, or perhaps the wrong endpoints for the trial. If the drug fails it gets dropped, which means that areas where it could have been useful are no longer investigated, and that's bad for patients. A basic problem is who decides on the best indications for a drug: scientists, who are basing their ideas on scientific data, or marketing executives, who are gambling on possible returns?"

Cost recovery of a simultaneous approach could also mean more expensive drugs, especially if they are lifesaving. However, "if the drugs work, society will pay", Sikora adds. "The problem at the moment is not so much the high cost of cancer drugs but their low benefit, which makes them cost-ineffective to health authorities. We are still measuring improvement in survival in terms of months, not years."

Some voices are now saying that the current regulatory process used by the US Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products, which relies on proven benefits in phase III trials (and which vastly increases the time and cost of drug development) needs to be changed radically.

"We need to get rid of phase III trials which provide very little extra, and sometimes even less, information than phase II trials", says Jones, "and replace them with better-designed phase II trials and regulation of postmarketing data. This would avoid drugs that may have been useful in some indications disappearing from the scene if they fail phase III trials for other indications. The simultaneous trial system does speed things up, but only within the current regulatory framework of drug development. What we need for real speed is to change that framework".

Carl Peck (Center for Drug Development Science, Georgetown University School of Medicine, Washington, DC, USA) agrees that change is needed. "We propose a clinical pharmacology intensive approach to derive causal evidence of effectiveness and safety, permitting early regulatory approval. [We have previously presented] the rationale for replacing traditionally required, redundant, empirical phase III data with scientifically sound phase II dose–response knowledge to support a phase III confirmatory trial. Such an approach should allow market approval in 3 years or less, as was routine for HIV protease inhibitors 10 years ago."

''WE NEED TO GET RID OF PHASE III TRIALS''

However, Silvio Garattini (Mario Negri Institute, Milan, Italy) warns: "New anticancer drugs should be submitted to the evaluation of the regulatory authorities only when two pivotal phase III studies are available, unless we are dealing with a miracle drug. These phase III trials should compare the new drug with the best available protocol of treatment for a given tumour".

Simultaneous trials might bring drugs faster to some patients. However, the issue remains as to whether new systems could bring them online even more rapidly without sacrificing safety. The challenge now is to find out.

Adrian Burton

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PODIUM

The Bottom Line

Professor Jim Cassidy

Professor Jim Cassidy (University of Glasgow, UK) has responsibility for clinical and laboratory work and his special interests include telomerase, DNA repair, drug resistance and molecular pharmacology of anti-cancer drugs. He is the guest editor of this issue's special section on the pharmacoeconomics of new cancer treatments.

How serious a problem are the new high-cost drugs causing?

It's one of the crucial challenges facing oncology. In 5 years' time, the 16 medicines now considered expensive (*EJC, this issue, p. 2887*) will cost as much as the current turnover of all drugs in all hospitals. But some of the talk of bankruptcy caused by these new drugs should be taken with a pinch of salt: a hospital or trust may have been heading towards bankruptcy anyway, and the high cost of drugs might be a convenient excuse. The cancer drugs budget in terms of the total budget is still not high, but it can be easy to focus on this one aspect of the budget.

How are the high costs affecting clinicians now?

Essentially, if something is expensive, its use will be regulated in some way. In the UK, regulation is enforced through NICE (National Institute for Health and Clinical Excellence), but there are similar organisations in other countries such as Germany and Australia. They bring pressure to bear not to use drugs considered to be overpriced.

Are clinicians equipped to deal with these issues?

Not at all, it is not part of what we do. Economists and managers should be regulating the costs of treatments. In truth, the issues are often passed down to the clinician facing the patient. It's an unhappy situation: when you have a disease like cancer, the last thing you want to hear is that someone doesn't value your life; or that benefit to you is not considered cost effective.

But the converse is important: if nearly every patient were given high cost treatments, we would not be in a position to treat anyone because the budget would be used up. Something has to happen; society has to make a decision on which things to fund.

Who should be responsible for taking difficult decisions?

Governments should get involved in an overt discussion. They should set out a list including everything from diabetes, through cancer to eye surgery, and say that the public needs to decide what the national health service is going to pay for. The Canadians have already done this. Politicians are hiding from this debate because it won't win votes but they will have to come round to it. There are going to be new drugs and the drugs budget is going up inexorably.

How well can the cost-effectiveness of drugs be measured?

Pharmacoeconomics is still a relatively young science and there isn't a consensus on the correct methodology, or the assumptions made to populate the model. The age of patients, for example, has a large impact on whether a treatment is considered cost-effective. We are learning along the way, and the methodology needs to be worked out in prospective randomised controlled trials. When we started using QALYs (quality-adjusted life years), there were many different methodologies; now there are just a handful. The same will happen in pharmacoeconomics.

Are cross-border inequalities surmountable?

Large differences in access to new drugs are driven by the philosophies of the country, the attitudes of public health care professionals, budgets, and the mix between public and private payments. The problems are surmountable but we will have to think out of the box to make it work. We need a Euro-NICE; and it's not impossible if the political will is there.

Individual countries' philosophies would determine the uptake of guidance from a Euro-institution. In southern Europe, people are more laissez-faire and drugs tend to be approved more quickly. In the north, people are more conservative and drugs are somewhat slower to come on to the market. You might imagine, because of the economics, that it would be the other way round.

What is the way ahead for pharmacoeconomics?

We need to insert economic questions into clinical trials and analyse the results with the same rigour we use to look at any other endpoint. We need to be able to say that a drug costs so much in terms of toxicity and so much in terms of money. It's not rocket science, we could do it.

What are you hoping the Special Section will achieve?

We're hoping to raise the level of debate about the whole issue, and to draw attention to the complex challenges in oncology. To take an analogy, when quality of life was first muted as an endpoint, it was thought boring, not worthwhile. We're at the same level now with economics: everyone is very aware of the issue, but being aware of it and actually doing something about it, are different matters.