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The Real Cost of New Drugs

Services and other treatments will have to be cut to pay for trastuzumab (Herceptin), say researchers in Norwich, UK. New guidance from the UK's National Institute for Health and Clinical Excellence (NICE) recommends the drug in early stage breast cancer. In the absence of additional funding, or any suggestion of which services to cut, medical professions are left with difficult decisions, they write (*BMJ* 2006;**333**:118–20).

"Nobody has suggested what treatments we cut in favour of Herceptin – not the media, medical advocates of the drug, the courts who upheld patient appeals, or NICE," they say. "Medical professionals ultimately have to make these difficult decisions."

The researchers estimate that the Norfolk and Norwich hospital will have to find Euro 2.9 million each year in drug costs alone to make Herceptin available to the 75 patients who may be eligible. This is 4 times the cost of treating 355 patients at the same hospital with other adjuvant cancer therapies – including oxaliplatin and rituximab – and with less potential benefit.

"These treatments have been proved to be clinically effective and their estimated cost effectiveness is far greater than that currently expected for Herceptin", they say. "The cost of giving Herceptin should not be measured in money alone, but also in the treatments that will have to be dropped to balance the books."

Further, NICE's decisions are susceptible to external pressures: "High profile patients, media bias, industry support and political gaming put considerable pressure on the National Health Service to offer this drug in early stage breast cancer."

NICE should be given the responsibility to decide what should be cut to fund newly recommended technologies, or the ability to allocate extra funds for implementation, or both. "Without these changes, Herceptin will not be the last controversial case of 'rationing by media'", they conclude.

But Dr. Martine Piccart-Gebhart (Institut Jules Bordet, Brussels, Belgium), President of EORTC, said that although the drug appears expensive, careful economic analysis, taking all factors into account, showed that the costs of giving it in early disease were "within the range of other medical treatments which have been accepted by society for a long time."

Economic analysis is complex, she said, but factors that need to be considered included lives saved, and the prevention of relapse, which is extremely expensive to treat.

Studies have clearly established that treatment with trastuzumab for one year is beneficial, Dr. Piccart-Gebhart said, but the studies were not optimal in that they did not address whether a full year's treatment is necessary. A Finnish study gave the drug for 9 weeks with "very interesting results", she said, and this duration of treatment would be cost-saving.

Further, improved translational research is the only way to identify more precisely which patients should be given the drug: probably only half the patients with *her2*-positive breast cancer benefit from trastuzumab.

"This is a lesson in the way we design and conduct trials. We only have one opportunity! We can't go back now and start a large trial looking at the optimal duration of treatment. As academic researchers, we are not always sensitive enough to cost aspects and translational research needs a lot more financial support than we have received so far," she said.

Aromatase Inhibitors in the UK

In November, 2006, NICE recommended the use of aromatase inhibitors anastrozole, exemestane and letrozole for the treatment of early oestrogen-receptor-positive breast cancer in postmenopausal women. Anastrozole is recommended for primary adjuvant therapy; exemestane for adjuvant therapy following 2 to 3 years of adjuvant tamoxifen therapy; letrozole for primary adjuvant therapy and extended adjuvant therapy following standard tamoxifen.

According to NICE, factors to consider when choosing the treatment include whether the woman has received tamoxifen before, the licensed indications and side-effect profiles of the individual drugs, and, in particular, the assessed risk of recurrence.

Dr Emma Pennery, nurse consultant at the charity Breast Cancer Care said the guidance "could make a real difference to thousands of postmenopausal women with hormone-receptor positive, early stage breast cancer." "We look forward to seeing this guidance implemented quickly to remove any barriers patients in England and Wales have faced in accessing these drugs wherever they live."

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Dasatinib Approved in Europe

Dasatinib (Sprycell) has been approved by the European Commission for the treatment of adults with chronic, accelerated or blast phase chronic myeloid leukaemia (CML). The approval, in November 2006, covers disease which is resistant or intolerant to prior therapy, including imatinib mesylate.

The drug is also indicated for the treatment of adults with Philadelphia chromosome positive (Ph+) acute lymphoblastic leukaemia (ALL) and lymphoid blast CML with resistance or intolerance to prior therapy.

Dasatinib has orphan drug status and manufacturer Bristol-Myers Squibb said it received rapid approval from the European regulatory authorities. It was previously approved in the US (June, 2006), India (August 2006) and Peru (October 2006).

Bcr-Abl is the key protein responsible for CML and Ph+ ALL, and the standard treatment, imatinib mesylate, blocks its activity. Resistance may develop either when the Bcr-Abl protein is overexpressed, or when mutations change its shape so that the agent can no longer work. Dasatinib inhibits the action of Bcr-Abl with all but one known mutation. (Resistance may also involve other proteins involved in cancer pathways, such as the Scr pathway.)

The approval was based on five phase II multi-centre studies in patients with resistance or intolerance to imatinib mesylate in all phases of CML or Ph+ ALL. The drug was found to have a predictable and manageable side-effect profile.

Professor François Guilhot (University Hospital la Milétrie, Poitiers, France) said that in a phase II study, responses were durable in the majority of patients with chronic phase CML who had become resistant to standard treatment. "It is worth noting that as early as in the Phase I study, haematologic and cytogenetic responses were observed in all phases of CML and in Ph+ ALL in the first 84 patients treated and followed for up to 19 months. Responses were durable across all phases of CML and Ph+ ALL."

Smoke from Domestic Coal Fires "is Carcinogenic"

Wood or coal fires used for cooking or heating are a source of carcinogens and improved ventilation in houses would reduce the lung cancer burden in large parts of the world's population, concludes a new IARC (International Agency for Research on Cancer) Monologue.

Over half the world's population, mostly in low- or medium-resource countries, uses wood or coal for heating and heating, often in unventilated spaces. IARC Director Dr Peter Boyle said that exposure to these emissions is experienced daily by hundreds of millions worldwide: "It is therefore of enormous public health importance that we call attention to the health risks of what is daily practice for so many people."

Occupational exposure to the products of coal fires has been known to cause lung cancer. Many studies – especially from China – now show similar effects from household use of coal. The Monograph concluded that there is sufficient evidence in both humans and experimental animals to conclude that indoor emissions from household coal fires are carcinogenic to humans (Group 1).

Fumes from domestic biomass fires (mostly wood but also charcoal, dung and unprocessed vegetal residue) are "probably carcinogenic" (Group 2A), as are emissions from high-temperature frying. (*IARC Monograph Vol 95. Household use of solid fuels and high-temperature frying. See http://monographs.iarc.fr/*).

Research in China has established that the risks can be greatly reduced by adequate ventilation (the construction of a chimney) and IARC says this "seems an obvious first public health measure to start reducing the lung cancer burden for large parts of the world's population. Changing cooking and heating methods should also be considered."

Products of incomplete combustion contain many particles, including known human carcinogens such as formaldehyde and benzene. Average indoor concentrations of particles <10 micrometres can be several milligrams per cubic metre; with peak concentrations 10 times higher. Dr. Boyle: "There are parts of the world where women and young children especially are exposed to these high levels of indoor air pollution for most of their day. Fortunately, these exposure levels can be greatly lowered and the cancer risk reduced."

Sunbeds "Clearly Increase Melanoma Risk"

People who first used sunbeds in their teens and twenties have a "clear increase" in melanoma risk, according to an IARC Working Group. Such users of artificial tanning facilities have a 75% increase in risk of melanoma.

"Young adults should be discouraged from using indoor tanning equipments, and restricted access to sunbeds by minors should be strongly considered," the group concluded (*Int J Cancer, 2006 doi:10.1002/ijc.22453*).

IARC was prompted to convene the Working Group by the French Ministry of Health, which expressed concern about the continuous increase of melanoma in France and worldwide. The number of cases doubles every 12 to 15 years in the most affected areas, IARC said.

A previous IARC Working Group concluded in 1992 that "use of sunlamps and sunbeds entails exposures that are probably carcinogenic to humans". The 2006 conclusions were stronger. Ever-use of sunbeds was associated with a 15% increase in melanoma but there was no consistent dose-response relationship. However, first-exposure to sunbeds before the age of 35 increased risk by 75%, it stated.

The conclusions were based on a systematic review of 19 case-control, cohort or cross-sectional studies. The review found an increased risk of squamous cell cancer in those who first used sunbeds as teenagers, but no association with risk of basal cell cancer. The data suggested detrimental effects on the skin's immune response and possibly on the eyes (ocular melanoma). It found no positive health effects: little if any protection against solar damage to the skin and no protection against vitamin D deficiency.

Smoking Bans Spread through Europe

New bans on smoking in enclosed public places are to come into force in 2007. The French and UK governments have set dates for the implementation of new legislation.

In Wales, the ban comes into force on 2nd April, 2007, and in England, from 1st July, 2007. In France, from 1st February 2007, workplaces except for the hospitality sector will be smoke free; from 1st February 2008, restaurants, bars and nightclubs will be included.

The moves follow the implementation of smoking bans in Ireland, Scotland, Italy, Norway and Malta. The Welsh ban proposes few exemptions; the English ban includes membership clubs, and work vehicles that are used by more than one person. Indoor smoking rooms, still common in workplaces, will no longer be allowed and staff will have to go outside to smoke.

UK Health Secretary Patricia Hewitt said, "Never has a health issue created such debate in Parliament, across government, through the business and the voluntary sectors and amongst the general public. And the more it has been debated, the more people have responded and pushed the limits to ensure that enclosed public places and workplaces in England will become wholly smoke free."

- Tobacco control policies are gaining ground throughout Europe. Earlier in 2006, Belgian researchers devised the Tobacco Control Scale to measure country's activities (*Tobacco Control 2006;***15**:247–53). It ranked 30 European countries by their total score out of a maximum possible of 100. Countries were assessed on their performance on 6 cost-effective interventions: higher taxes, public place bans, advertising bans, consumer information, warning labels and help for smokers who wish to quit.

At the time, only four countries (Ireland, UK, Norway, Iceland) scored 70 or more, with an 8-point gap (most differences in scores were small) to the fifth country, Malta, on 62. Only 13 countries scored above 50, 11 of them from the European Union. Ireland had the highest overall score (74) and Luxembourg was bottom (26 points). However, even Ireland did not increase tobacco taxes in 2005, for the first time since 1995.

The researchers said that most countries could improve their score and they hoped the scale "will be useful in encouraging countries to strengthen currently weak areas of their tobacco control policy."

Smoking less "Doesn't Help"

Heavy smokers who halve their cigarette consumption do not significantly reduce their risk of premature death, say Norwegian researchers. Advising smokers to cut down "may give people false expectations".

The prospective cohort study included 51,000 men and women who were aged between 20 and 34 in the mid-1970s. They were initially assessed for cardiovascular risk factors, screened again twice at intervals of 3 to 5 years, and observed for an average period of 20 years (*Tobacco Control 2006;***15**:472–80).

"Reducers" smoked more than 15 cigarettes a day, and cut this by more than half at the second check; "heavy smokers" consumed more than 15 cigarettes a day.

Men who cut back had slightly lower death rates from all causes than the heavy smokers in the first 15 years, but later, death rates were comparable. Female reducers had clearly higher death rates than heavy smokers, both from any cause and from smoking-related cancer. The researchers say this could be ascribed to chance.

Lower cigarette consumption at the second check could be due to under-reporting. Compensatory smoking (deeper inhalation and shorter butts) may also have an effect. But reducers had a lower level of serum thiocyanate, indicating that a substantial proportion of the reduction is real.

Cutting down may be a useful temporary measure in systematic smoking cessation, but it is "imperative to reassess this recommendation as a permanent solution", the researchers conclude.

Dating and Smoking in Children

Children who have a boyfriend or girlfriend in their pre-teen years are at least twice as likely to become smokers before leaving school, say London researchers. They hope that understanding the personalities of young smokers will help them unravel children's motivation to take up smoking.

Being an early "dater" was a significant predictor of later smoking uptake, even after controlling for potential confounding factors such as pubertal stage. The association was very strong in girls: those who were dating in their pre-teen years were 9 times more likely than their non-dating contemporaries to have started smoking at age 13, and 3 times more likely to have started smoking by age 16. Boys who were dating at age 11 and 12 were, respectively, 6 times and twice as likely to take up smoking as their non-dating peers (*Addiction 2006;***101**:1805–13).

Lead author Jennifer Fidler (University College London, UK) said, "This is particularly interesting because recent figures show that while the number of 14 to 15 year old boys admitting to smoking has nearly halved to a quarter, the number of girls of the same age who say they smoke has risen to nearly half."

The 5 year prospective study included 2000 London school children. They completed anonymous questionnaires about their behaviour and smoking from year 7 (age 11–12) to year 11 (age 15–16). Their saliva was analysed for cotinine.

The researchers suggest that aspects of dating at a young age, such as image formation and popularity among peers, result in smoking. Alternatively early dating may merely precede smoking and both may arise from the common cause of "aspiring to be an adult".

Early daters could be a key target for smoking interventions which highlight the social undesirability of smoking, the team concludes.

Should HPV Vaccination be Compulsory?

A new round of polarising debates will be ignited by moves to make the vaccine against human papillomavirus (HPV) compulsory, according to ethicist Dr. James Colgrove (Center for the History and Ethics of Public Health, Columbia University, New York, USA).

The Advisory Committee on Immunization Practices of the Centers for Disease Control and Prevention has recommended that the vaccine be given routinely to girls at 11 or 12 years of age but took no position on whether vaccination should be required by law. The state senate in Michigan has already passed a bill proposing compulsory vaccination (it awaits consideration by the house). Other states are likely to follow this lead.

In a perspective (*N Engl J Med* 2006;**355**:23;2389–91), Dr. Colgrove writes that support for mandatory vaccination is strongly influenced by the perception of HPV as a women's health issue. Women in Government, a Washington-based bipartisan organisation of female legislators, is leading a push to make HPV vaccination compulsory in every state, he says.

On the other side, opposition will come from a far wider range of constituencies than religious conservatives, worried about threats to sexual abstinence. Vaccine requirements "have been resisted in recent years on a wide range of philosophical, political, scientific and ideological grounds," he writes.

"Laws making vaccination compulsory raise unique ethical and policy issues". Minors have a right to be protected against vaccine-preventable illness, and requiring vaccination by law will almost certainly achieve more widespread protection than policies relying on persuasion and education.

But HPV is not casually transmitted, unlike measles or pertussis, and in the absence of potential harm to a third party, such laws "may be considered unacceptably paternalistic".

Dr. Colgrove concludes: "Although issues of religion and adolescent sexuality have dominated the discussion, the move to require HPV vaccination raises broad questions about the acceptability of mandatory public health measures, the scope of parental autonomy, and the role of political advocacy in determining how preventive health measures are implemented."

Protocol for HIV/AIDS in Europe

The World Health Organization (WHO) has issued treatment and care protocols for HIV/AIDS for the European Region. "These protocols will help to address the pressing need for a comprehensive and consistent approach to treating and care for people with HIV/AIDS in all 53 member states of the WHO European Region," said Dr. Marc Danzon, WHO Regional Director for Europe.

The 13 protocols each have a specific focus such as HIV/hepatitis co-infection and are available on the WHO Regional Office website (www.euro.who.int/aids/).

An estimated 2.44 million people in the European region are living with HIV/AIDS. The situation is particularly serious in the eastern parts of the region: Estonia, the Russian Federation and Ukraine. Non-sterile injecting equipment is the predominant risk factor in the Russian Federation.

Symptom Check List for Ovarian Cancer

A simple evaluation of recent symptoms may be sufficient to detect the early stages of ovarian cancer, researchers say. It could be the basis for a rapid, cost-effective screening tool.

Dr. Barbara A Goff (University of Washington, Seattle, USA) and colleagues compared the clinical history of women at high risk for developing ovarian cancer, and women already diagnosed with ovarian cancer. They devised a basic symptom index to screen for ovarian cancer (*Cancer 2007 doi:10.1002/cncr.22371*).

The checklist included complaints of pelvic or abdominal pain, increased abdominal size or bloating, or difficulty eating and feeling full. Symptoms that were present more than 12 days per month and for less than one year were 57% sensitive for early disease and 80% sensitive for advanced cancer. They were 90% specific for women over 50 years of age, and 86.7% for younger women.

Dr. Goff plans to evaluate a simple 3-question screening questionnaire in general clinical practice.

In an accompanying editorial (*Cancer 2007 doi:10.1003/cncr.22414*), Sherry Salway Black (Ovarian Cancer National Alliance, Washington DC, USA), writes that the development of a screening blood test would be "the real key" to early detection. "Until there is a valid screening test, the symptom index could serve as important role in detecting cancers, and after a test is identified, the index could be a tool used in combination with other methods to contribute to early detection."

Patients' Views on Conflicts of Interest

More than 70% of patients in clinical cancer trials say they would still have enrolled if they had known about any researchers' or cancer centres' financial ties. However the vast majority (84%) felt that links with drug companies should be disclosed either to patients themselves or to an oversight system.

Researchers interviewed 253 patients in cancer trials at 5 US medical centres and found that more than 90% expressed little or no worries about financial ties that researchers or institutions might have with drug companies (*N Eng J Med* 2006;**355**:*2330–7*).

They suggest that for cancer patients, concerns about health and getting the best care seemed to predominate. "It is probably psychologically essential for such patients to trust that their doctors and cancer centres would not let financial ties compromise their medical care."

The patients in the study – typical of those in cancer research trials, the authors say – tended to be well-educated, financially secure, older, and white. This may have biased the study towards an overestimation of concern. "Only among patients with graduate training were the majority worried about or wanted to prohibit such financial ties," they said.

PODIUM

Telemedicine in Wales

Delyth Lewis

Delyth Lewis is Telemedicine Project Manager for the Ceredigion & Mid Wales NHS Trust. For the past 2 years she has developed and implemented the use of telehealth across National Health Service (NHS) sites in Ceredigion. Since September 2005, she has managed the implementation of telemedicine across the South West Wales Cancer Network.

Why do you need telemedicine in a country as small as Wales?

When an UK expert advisory group on cancer (Calman Hine, 1995) recommended a new way of working: cancer centres, minimum standards, multidisciplinary teams and cancer networks, it created a problem for Aberystwyth in mid Wales. The cancer network serves a large geographic area, urban and rural, including a lot of isolated farms. The main cancer centre is 75 miles away and takes 2 hours by car. The road infrastructure is poor and there is no direct rail link; the train journey from Aberystwyth to Swansea involving 3 changes of train.

How can telemedicine help?

Our Trust's medical director, Dr Alan Axford, visited telemedicine projects in the United States and thought we could utilise some of the ideas. In 2000, we had the first virtual multidisciplinary team meeting. We had conferencing equipment in Aberystwyth and in Swansea and linked the 2 specialist multidisciplinary teams. They discussed treatment options and management plans, and the technology allowed sharing of radiology imaging and pathology slides, exactly as if the whole team were in one room.

Are there other advantages?

Video conferencing reduces travelling, and allows us to organise educational meetings for the nurses in our network. They meet virtually; without the video link, meetings would never happen.

Virtual meetings allow people to build good working relationships within the multidisciplinary team. Specialist nurses give their input and seek specialist opinion on matters about which they would never contact a consultant.

People are more focussed in teleconferences. If a meeting is scheduled with the Swansea team, each hospital may be allocated a half-hour slot and they have to use the time efficiently.

What problems have you encountered?

We had to find the funding for the teleconferencing equipment. Glynis Tranter, manager of the South Wales cancer network, took on the fundraising and we have received a grant from the Welsh Assembly.

The technology at first relied on an ISDN telephone line, so we had to pay call charges and the line was not always reliable. Now we use an IP network, calls are free, and it is much more user-friendly.

Has the staff had to learn new skills?

Video conferences require discipline. Up to 6 sites can be linked but only one site can speak at a time. If there is one person in one room, and a group elsewhere, the group has to be careful not to forget the person in the remote room. There is microphone etiquette: people have to speak into it, take care not to turn their back on it – and learn not to shout!

What are the limitations?

Telemedicine is complementary to normal medicine; it can never replace the doctor who can examine patients. Video conferencing also cuts out the networking that often takes place during coffee breaks at meetings. Meetings involving a lot of paperwork can get complex. The feedback so far suggests that for quarterly meetings, 3 can be virtual, but one should be face to face.

How have patients reacted?

We have started using it in accident and emergency and patients do not seem to object. Nurses in community hospitals can ask for a second opinion from the main casualty department via a video consultation. We are also using telemedicine in follow-up appointments, after discharge. The consultant is based at the centre; nurse and patient in the community hospital. Patients feel they have the attention of both nurse and doctor and can stop and ask the nurse for clarification at any time. In normal consultations, nurses often have other jobs to do.

What new areas are you considering?

We want to further develop the telemedicine services across the South West Wales Cancer Network so that we link microscopes in between laboratories. A pathologist working singlehanded can then get a second opinion from a colleague in another hospital.

In palliative care, we link to a Marie Curie centre, which is an education centre. Our palliative care team is nurse-led, as we do not have a consultant, but with this link we can access best practice seminars and we are using it as a distance learning tool. We would like to expand the video consultation to link the palliative care team with patients at home in the later stages of life. There is a lot of work to be done on security issues – we cannot allow home computers access to the NHS database – but we are looking at it.