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## Smoking in Europe

Levels of smoking across Europe are not falling significantly despite the anti-tobacco policies now in force in most countries, according to a new report from the World Health Organization (WHO). "Substantially stronger measures" will be needed to bring about further decreases in the prevalence of smoking, it states.

The *European tobacco control report* from the WHO's Regional Committee for Europe stated that smoking prevalence has stabilised or is decreasing in most western European countries. It has also started to decrease in some countries in the east, although generally only among men, while a slight rise in prevalence among women is being recorded in some states.

At the end of 2005, smoking prevalence in the European region was estimated at 28.6% (40% among men and 18.2% among women). This compares with 28.8% in 2002 (40.9% among men and 17.8% among women). These changes are reflected in a region-wide fall in lung cancer mortality among men. Lung cancer rates among women are still increasing.

*'A MAJORITY OF SMOKERS FAVOUR TOUGHER CONTROLS'*

Prevalence in western countries has "reached a level from which it will be difficult to show a further decrease unless substantially stronger measures are implemented," the report states. Some eastern countries, where smoking shows no real signs of decreasing "need to continue and in many cases accelerate their implementation of baseline recommendations."

Smoking among adolescents remains a problem. On average 24% of 15-year olds smoke (24% of boys and 23.5% of girls). In many western European countries the prevalence of smoking among girls exceeds that among boys.

Lower socioeconomic groups are also vulnerable. Throughout the Region, smoking is increasingly concentrated in disadvantaged groups which is "leading to a widening gap in current and future health outcomes. Smoking remains a major contributory factor to the gap in mortality and healthy life expectancy between the most and least advantaged," the report states.

The report noted the "strong resistance by the tobacco industry to control or regulation justified by public health concerns. In parts of the European Region where smoking prevalence is stabilising, attempts to maintain the rates of tobacco use and to increase profits have become a major preoccupation of the industry."

Despite this, there is significant and increasing public support for national and international efforts to develop and strengthen legislation and regulations for tobacco control. "It is not only a large majority of non-smokers that support stronger measures: a majority of smokers too favour tougher controls. One important policy consideration is, therefore, that governments and society need to use the current momentum to create a turning-point in combating the tobacco epidemic in the Region."

The introduction of smoke-free legislation in public places has been one of the most visible improvements since 2004, and most countries have made progress in banning advertising, increasing the size of health warnings on packets, and increasing taxes. The report urges countries to consider tobacco tax and pricing issues, and to explore new or unfamiliar strategies such as a reduction in the number of points of sale. They also need to hold to the principle "that governments and public health authorities refuse offers of co-operation with the tobacco industry in framing their tobacco control policies."

For the future, policies need to be tailored to reach vulnerable and lower socioeconomic groups. Tobacco cessation programmes need to be implemented and evaluated and improvements in prevention of relapse need to be made, as rising numbers of smokers go through cessation services or use nicotine replacement therapy.

The report concludes that the 2002-2006 period has seen important progress in tobacco control policy in the Region but that "weaknesses in the implementation of new policies require urgent attention." The tobacco epidemic has in general stabilised. "The consequences are, however, still devastating for public health and countries need to strengthen their policies," it concluded.

*The full report is available at www.euro.who.int/Document/E89842.pdf*

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## A breath test for lung cancer?

A colour sensor breath test could eventually become an inexpensive test for lung cancer, US researchers say. The test, which analysed exhaled breath with a colorimetric sensor array, picked up lung cancer with "moderate accuracy" (*Thorax 2007; doi:10.1136/thx.2006.072892*).

Metabolic changes in non-small cell lung cancer (NSCLC) cells cause changes in the production and processing of volatile organic compounds, which are then breathed out. The test is a chemical colour sensor which detects these tiny changes in the chemicals of the breath of people with lung cancer.

The study included 49 people with NSCLC, 73 with other respiratory diseases such as chronic obstructive pulmonary disease, and 21 who were healthy. The research team used the sensor results from 70% of the study participants to develop a predictive model, which was tested on the remaining 30%.

It predicted the presence of cancer in almost 3 out of 4 of those with NSCLC, regardless of age, gender, or stage of disease. "Ultimately, this line of investigation could lead to an inexpensive, non-invasive screening or diagnostic test for lung cancer," the researchers concluded.

## Vaccine trial

Merck has started a phase III trial of its liposome vaccine, Stimuvax, in patients with stage III NSCLC. The trial is called START (Stimulating Targeted Antigenic Responses To NSCLC) and will assess safety and efficacy.

More than 1300 patients with unresectable stage III NSCLC are expected to be included. Patients will have had a response or stable disease after at least two cycles of platinum-based chemotherapy.

The vaccine is designed to induce an immune response to cancer cells that express MUC1, an antigen widely expressed on common cancers. Merck says that START is the first phase III study to evaluate a cancer vaccine for this indication.

# NICE says no to erlotinib

The National Institute for Health and Clinical Excellence (NICE) in England has not recommended erlotinib (Tarceva) for the treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC). The Final Appraisal Determination (FAD) concluded that erlotinib "could not be a cost effective use of NHS [National Health Service] resources when compared with either docetaxel or best supportive care."

The ruling puts England out of kilter with Scotland, where erlotinib has been approved since June 2006 for the same indication after failure of at least one prior chemotherapy regimen. The drug is also available in other parts of Europe.

Manufacturer Roche has announced its intention to appeal "on the basis that the evidence submitted has been assessed neither fairly nor appropriately and that the proposed guidance as it stands is perverse in the light of the evidence made available to the NICE Appraisal Committee."

Professor Nick Thatcher (Christie Hospital Manchester, UK) said: "Other European countries have had access to this treatment for over a year and it is very frustrating that English patients are once again losing precious time waiting for Tarceva to be made available to them. It is critical that NICE work with Roche to find a way to make this important treatment available to all eligible patients as soon as possible."

The FAD stated that patients currently receiving erlotinib have the option to continue therapy until they and their clinicians consider it appropriate to stop.

Clinical specialists giving evidence reported that the patients most likely to benefit from erlotinib were female non-smokers of South Asian ethnicity. The committee stated that

*'ENGLISH PATIENTS ARE ONCE AGAIN LOSING PRECIOUS TIME'*

current evidence "remains too weak to infer effectiveness or cost effectiveness in this subgroup". It recommended further research into subgroups for whom erlotinib may provide greater benefit.

The committee left the door open for a revised decision early next year: "Given the rapidly changing evidence base for erlotinib, the committee advised that the guidance should be considered for early review. The guidance on this technology will be considered for review in February 2008."

● This decision follows other controversial – and contested – recommendations on new cancer treatments. On 20th October, 2006, a FAD from NICE did not recommend bortezomib (Velcade) monotherapy for the treatment of patients with relapsed multiple myeloma.

The decision was taken on cost grounds. The Committee in this case concluded that bortezomib monotherapy is clinically effective compared with high-dose dexamethasone, but stated: "it has not been shown to be cost effective".

Like erlotinib, this drug is available to patients in Scotland, and those in England who are currently receiving it, can continue therapy.

Four appeals were submitted: by manufacturer Janssen-Cilag, by the UK Myeloma Forum, jointly by the charities Myeloma UK, Cancerbackup and Leukaemia CARE, and, again jointly by the British Society of Haematology and the Royal College of Pathologists. The appeal was heard on 8th February, 2007, but several weeks later, no decision had been announced. The guidance on bortezomib is due to be considered for review in October 2007.

● In June 2006, Eli Lilly's pemetrexed disodium (Alimta) was "not recommended for the treatment of malignant pleural mesothelioma except as part of ongoing or new clinical trials" in an FAD by NICE.

Following appeals, the Panel met on 15 December, 2006, and upheld some of the points made. The appraisal was sent back to the Appraisal committee for discussion on 6th March, 2007 after which an Appraisal Consultation Document (ACD) was due to be sent to consultees and commentators. Comments on the ACD will be discussed by the Committee on 8th May, 2007, at which stage another FAD will be produced. The earliest launch of final guidance will be August/September 2007.

# EUROFILE

## Are we doing the right phase III trials?

Researchers at the Memorial Sloan-Kettering Cancer Center (NY, USA), suggest that flaws in the preparation of phase II oncology trials are leading to the testing of the wrong candidate drugs at phase III (*Clin Cancer Res* 2007; 13: 972–76). For patients, this means lost hope; for pharmaceutical companies, huge amounts of money sunk into bad investments.

Candidate drugs often underperform in phase III trials. The last 2 months alone have seen disappointing results for canfosfamide in non-small-cell lung and ovarian cancer, and for N,N-diethyl-2-[4-(phenylmethyl) phenoxy]-ethanamine in advanced breast cancer; this trial was halted due to poor interim results. The new report suggests one reason for such setbacks might lie in the inadequate statistical design of phase II trials, the job of which it is to decide whether a drug should proceed to phase III testing. "If we fail to set the null hypothesis correctly in phase II trials we could end up testing the wrong drugs at phase III", explains lead researcher Andrew Vickers. "You can think of the null hypothesis as a bar that a drug has to jump over. To work out how high to set the bar, you often need historical data. For example, if historical data suggest that standard chemotherapy is associated with 50% survival at 1 year, then a phase II trial of chemotherapy plus a novel targeted therapy might be designed so that a phase III trial is recommended only if 1-year survival is somewhat better than 50%. Clearly we have to be pretty sure about our historical data to set the right bar." However, Vickers' team reports that nearly half of the 70 phase II trials assessed that needed historical data cited no source. Furthermore, around three-quarters of the trials that did cite historical data did not do so appropriately.

"You can't just pick a figure out of the air", explains Vickers. "For example, if we choose a null response rate of 20%, when in fact the historical data show that the normal response rate is 40%, we have a good chance of sending an ineffective drug to phase III." Indeed, nearly 80% of the trials that did not reference their historical data appropriately suggested the agents they studied were worthy of further investigation, while only 33% of the trials showing more careful use of historical data did so.

*'FLAWED PHASE II TRIALS MEAN THE WRONG DRUGS GO INTO PHASE III'*

Frustration at phase III might also result from case mix problems. The amount of risk associated with patients involved in the different phases of drug trials commonly differs. "Yet, not one phase II trial we examined used a statistical method to adjust for case mix", says Vickers.

Phase III trials can also provide disappointing results because of changes in endpoint selection, poor recruitment, or poor treatment com-pliance. Additionally, the pressure on pharmaceutical companies to turn a profit could lead them to undertake risky phase III trials, hoping for a positive outcome even in the face of dubious scientific support. "There is some financial pressure to get trials done as the start of a study is usually woven into investment strategies by external investors. This is most obvious when dealing with small to medium size pharmaceutical companies", explains James Cassidy (Beatson Oncology Centre, Glasgow, UK). "If the phase II [results are] overoptimistic they encourage the company to proceed into larger scale trials, but unfortunately they [often set] unrealistic outcome targets and utilise sample sizes that are too small to detect smaller but still clinically meaningful benefits."

"Statistical methods exist for determining valid sample sizes", explains Judith Bliss (Institute of Cancer Research, Sutton, Surrey, UK), "but many trials have been undertaken with numbers far too small to allow the reliable detection of clinically worthwhile benefits. Without the right preparation you're unlikely to get reliable results". However, she explains, "we have made advances in the way we do trials over the last 10 years. The average sample size has increased [and there has been] better appreciation of the size of potential benefit one can reasonably expect". Nonetheless, Bliss is concerned about the future. "Many of the recent successes have emanated from trials which have been a true partnership between academic trials groups and interested pharmaceutical companies. Increased regulation and bureaucracy are threatening the willingness of partners to continue [with this model], which has brought together academic independence and rigour with early access to potentially exciting new therapies. I cannot see how a breakdown in such methods of conducting research will benefit patients."

*'MANY TRIALS ARE FAR TOO SMALL TO DETECT WORTHWHILE BENEFITS'*

Even though some voices are calling for phase III trials to be abandoned (*Lancet Oncol* 2006; 7: 798), they remain the gold standard for testing candidate drugs. Setbacks might be a natural part of the development process, but patients with cancer cannot afford that we suffer too many. Making sure the right phase III trials are undertaken is one way of offering them more hope.

*Adrian Burton*

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## 'Improvements needed' in end-of-life care

Substantial restructuring of traditional hospital systems is needed to meet the needs of those with serious chronic illnesses, say US researchers. End of life care is "fragmented and inefficient" and regions should "deliberate on priorities, set goals, demand excellence and monitor progress" *(BMJ 2007 334:511–513)*.

A fundamental shift in attitude is required, they say: "Healthcare systems are designed as if disability and ill health were aberrations, rather than a phase that lasts months or years near the end of our lives, despite the contrary evidence all around us."

Hospice programmes have been "an important and instructive initial response" but they do not meet most patients' needs. It is increasingly accepted that end of life care should encompass all people sick enough to die, even through some will live in fragile health for some years.

The authors identify 3 trajectories in fatal chronic illness. In the first – typical of common solid cancers in adults – patients have good function until a short period of relatively predictable decline in the last weeks or months. Planning ahead and aggressive management of symptoms at home often prevent unnecessary admissions to hospital and interventions.

The second trajectory – typical of chronic heart failure – is "chronic organ system failure with slow decline punctuated by dramatic exacerbations that often end in sudden death". The third is poor long term function and slow decline, as occurs in some chronic cancers which present as a co-morbidity in advanced old age.

Some aspects of care are universally important; but patients' priorities may differ according to their trajectory, and a reformed system could be built around typical patient situations. "Customising and reorganising care to match the needs, rhythms and situations of these three trajectories offers a promising way to improve outcomes for patients sick enough to die."

# Capecitabine in gastric cancer

The European Committee for Medicinal Products for Human Use (CHMP) has given capecitabine (Xeloda), in combination with platinum-based chemotherapy, a positive opinion for first line use in patients with advanced gastric cancer.

The recommendation is based on results from two phase III studies: ML17032 and REAL2. The ML17032 study included 316 patients in 46 centres in Asia, South America and Europe. It found that time to progression was at least as long among patients receiving capecitabine/cisplatin as among those on 5-FU/cisplatin. The second study, REAL2, included 1002 patients with advanced gastro-oesophageal cancer in 61 centres, mainly in the UK. It found that those who received capecitabine with oxaliplatin and epirubicin lived significantly longer than those receiving the standard combination of epirubicin, cisplatin and 5-FU.

Capecitabine is an oral treatment which reduces the time patients need to spend in hospital, from 5 days every 3 weeks with intravenous treatment, to 1 day every 3 weeks.

The drug is already approved in the EU and US for first-line monotherapy of metastatic colorectal cancer and adjuvant treatment of stage III (Duke's stage 3) colon cancer. It is licensed in combination with docetaxel in women with locally advanced or metastatic breast cancer whose disease has progressed following intravenous chemotherapy with anthracyclines. Roche, the manufacturer, is seeking further indications in several countries worldwide.

# Orphan status for fenretinide

A previously shelved drug has been granted orphan status by both the Committee for Orphan Medicinal Products at the European Medicines Agency (EMEA) and by the US' Food and Drug Administration (FDA).

Fenretinide, which is now out of patent, was first made in the 1970s by Johnson & Johnson as a possible treatment for breast cancer, but never brought to market. Cancer Research UK has now been granted exclusive marketing rights for the drug for use as a possible treatment for a group of rare childhood cancers.

*'MANY YOUNG PEOPLE STILL SUCCUMB TO ESFT'*

The drug, a vitamin A analogue, has been studied by research groups in various types of cancer, including the Ewing's sarcoma family of tumours (ESFT), rare cancers affecting around one in a million young people (up to 24 years old) every year in the European Union. It is usually diagnosed in adolescence.

Laboratory studies at University of Leeds, UK, demonstrated that fenretinide significantly delayed tumour growth in models of bony Ewing's sarcoma and soft tissue peripheral primitive neuroectodermal tumour (pPNET). These promising results convinced the charity to apply for orphan designation for the use of fenretinide in the two categories of ESFT.

Phase I studies of fenretinide have already been carried out in adults and children. Dr Ian Lewis (St James's University Hospital, Leeds, UK) will be leading the phase II trial. He said: "A young person currently diagnosed with one of these forms of tumour will be treated with a cocktail of general chemotherapy drugs, surgery or radiotherapy. Despite improvements in treatment, many young people still succumb to ESFT. If we can confirm the effectiveness of fenretinide, it could significantly improve outcomes for this rare group of cancers."

The designation should accelerate the approval process of the drug, which is out of patent, and give Cancer Research UK, along with any future development partner, 7 and 10 years of market exclusivity in the US and EU, respectively. Other groups are currently investigating fenretinide. It has been compared with tamoxifen in phase III clinical trials in breast cancer, and is also being developed for use in neuroblastoma.

# PODIUM

## Quality of life among older patients

*Dr Lara Maria Pasetto*

*Dr Lara Maria Pasetto is an oncologist at the Istituto Oncologico Veneto (IOV), Padova, Italy. She has a special interest in cancer in the elderly and her paper, "Quality of life in elderly cancer patients" will be published in a forthcoming issue of EJC (doi:10.1016/ejca.2006.11.023).*

**What distinguishes quality of life issues in the elderly age group?**
Quality of life is usually poorer among elderly patients than among younger age groups. Many live in residential homes rather than with their family, some are depressed or confused, and they may have diseases other than cancer, which require many medications (polypharmacia). Their financial situation tends to be worse than for younger people and their educational level lower. Everything is more difficult for them.

**How far do treatment aims differ in different age groups?**
Now that life expectancy has increased, we have elderly people living to 80 or 90 years. They should therefore have the same opportunity to be treated as younger people do. Other medical problems are not a reason for avoiding treatment even if they could determine patient prognosis and overall survival; these problems could influence the choice of treatment.

**You say that age is a complex process?**
Age is certainly not only a chronological, but a biological process too. Elderly patients are a heterogeneous group and should always have a comprehensive geriatric assessment (determining whether patients are fit, vulnerable or frail), which reveals depression and mood, the life they lead and their performance status. Family background and educational level can also influence the assessment. This overall classification may help doctors determine different patients' prognosis and the best treatment, with fewest side effects. In fact, the majority of elderly cancer patients should be treated; elderly patients with breast cancer, for example, can receive hormonal therapy even if they are frail.

**How important are clinical trials among elderly patients?**
The age limit for participation in clinical trials was, until recently, 70 years. Elderly patients can now be included in trials more than once but so far data have been extrapolated from studies among mixed-age populations. Elderly patients have more and different problems from younger people and it would be useful to design and carry out trials exclusively for them. Studies could examine how the factors in the geriatric assessment change when patients receive chemotherapy, whether this treatment is really useful, and whether it improves quality of life. Trials devoted to elderly patients are the only way to further our understanding of psychological and physical aspects of cancer in this age group and to determine whether improvements in survival or response are related to improvements in quality of life.

**Is quality of life an endpoint in itself?**
It is, or it should be. It is fundamental to evaluate quality of life in elderly patients. A patient of any age with rectal cancer may find a colostomy distressing. But an elderly patient may need practical help to deal with it. They are more often isolated, and without help from family, this can have a detrimental impact on their quality of life.

Younger patients with metastatic colorectal cancer usually receive third or fourth line treatment, but elderly patients don't. If chemotherapy improves quality of life, it would be an indication to continue. But if best supportive care gives a better quality of life, we would obviously avoid chemotherapy and may improve the supportive care.

**Loss of independence seems to be a major problem in this age group?**
A patient receiving chemotherapy is dependent on family. Younger people surrounded by family are more often autonomous, self-sufficient and able to deal with the side effects of treatment. Elderly people receiving chemotherapy may not be able to get to the hospital by car, or by bus. Side effects can be worse for them, and if they are not addressed, patients may start to avoid chemotherapy, especially if they live alone.

**Do we need a special definition of quality of life for elderly?**
We need special assessments. Many of the tests include questions which are not relevant to elderly patients, such as whether they have been able to work as usual, or how the disease has affected their financial situation. But elderly patients usually don't work, and may not understand the question about finances, especially if their educational level is not high. They might be asked if they are able to remember things, but even healthy elderly people are less able to remember things than younger people. Some questions should be changed to make them more appropriate for the elderly, and the tests should be simpler, especially where they have to be completed by patients themselves.

**Is a quality of life assessment necessary to give individualised care?**
Quality of life assessments give patients the opportunity to indicate how they live, how they feel, how well they sleep, dream, eat and so on. They can help clinicians assess the relative importance of symptoms to a patient and to plan and modify the best treatment strategy.