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Herceptin: Getting the price right

Health care authorities should not rush to prescribe Herceptin® (trastuzumab) for early breast cancer without first calculating budget implications and working out for which patients treatment is cost-effective, conclude Belgium health economists in *Annals of Oncology* (published online 30 November).

Health economist Mattias Neyt and colleagues from Ghent University, caution that using Herceptin® as adjuvant therapy in early disease will impose a major financial burden on healthcare systems because of the high drug price, the long duration of treatment and the large number of women who would be eligible.

The team undertook an economic evaluation of adjuvant Herceptin® based on a group of patients aged over 50 with stage III breast cancer (locally advanced node positive) receiving trastuzumab as administered in the Breast Cancer International Research Group (BCIRG 006) trial. Researchers calculated costs of Herceptin® compared with standard treatment from the hospital's perspective using the micro-costing method.

Results showed total costs for doxorubicin and cyclophosphamide followed by docetaxel and trastuzumab was €45 034 and that treatment with docetaxel, carboplatin and trastuzumab cost €47 765. Almost 80% of costs were due to the addition of Herceptin. Further costs for the testing of HER2 gene expression (€167), and left ventricular ejection fraction tests to identify potential cardiac complications ($7 \times €55$) also had to be taken into account.

Cost savings for preventing metastatic disease, said Mr Neyt, will be explored further after the results of the BCIRG study are presented at the San Antonio meeting in December. The team found that depending on the health gains and/or price discount, an acceptable incremental cost-effectiveness ratio could be reached. These health gains will depend on the subgroup of patients being studied.

Careful resource planning will be required, say the authors, to ensure cost-effective innovations are not denied to patients. "This means countries should not rush into prescribing it before working out the implications very carefully and being prepared to reallocate resources, get rid of other treatments that are no longer cost-effective and drive a hard bargain over the price of the drug," said Mr Neyt, adding pharmaceutical companies need to appreciate that if they lower their price this will increase volumes of patients treated.

(see p 123 Podium)

Study gives snap shot of future challenges

Fewer middle-aged people are dying from cancer, while the number of new cases remains stable, concluded a study presented at the Britain Against Cancer Conference (24th November) in Westminster, London.

In the study Cancer Research UK and the UK Association of Cancer Registries (UKACR) analyzed the latest trends among people aged between 35 and 69 in the UK. Professor David Forman, the chair of the UKACR, who led the study, commented: "It's very important to look at cancer trends in younger adults, so we can see how the spectrum of cancer is changing. Having 10-year data has enabled us to do this for the first time for the UK as a whole."

The statistics showed:

- The current four major cancers (lung, breast, bowel and prostate) will continue to dominate.
- Fewer people are dying of cancer every year, with deaths rates having fallen by around 2.4% each year for the past 10 years.
- Prostate cancer incidence has more than doubled in 10 years, the dramatic rise in incidence is largely due to the increase in PSA testing.
- The number of new cases of women is falling in 35–69 year olds, indicating we are approaching the peak of cases in women of all ages. Rates are already falling in men.
- The number of melanomas diagnosed in the UK continues to rise, with incidence rates increased by 35% in men and 22% in women.
- The incidence of mouth cancer increased by 23% in men and 24% in women.
- Stomach cancer death rates have fallen by 39% in men and 45% in women.
- Bowel cancer deaths over the last 10 years fell by 22% for men and 26% for women.

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Prevention ignores risk factors

More than one third of the world's cancer deaths in 2001 stemmed from nine potentially modifiable risk factors, with smoking and alcohol playing a leading role, concluded a study published in *The Lancet* (2005; **366**:1784–93).

"With respect to reducing mortality, advances in cancer treatment have not been as effective as those for other chronic diseases; effective screening methods are available for only a few cancers," write the authors, led by Dr Goodarz Danaei, from the Harvard School of Public Health (Boston, Massachusetts). "Primary prevention through lifestyle and environmental interventions remains the main way to reduce the burden of cancers."

The study, by the Comparative Risk Assessment collaborating group (Cancers) from the Harvard School of Public Health and the Initiative for Global Health at Harvard, estimated mortality from 12 types of cancer attributable to 9 risk factors in 7 World Bank regions for 2001. The nine modifiable risk factors considered were high body mass index, low fruit and vegetable intake, physical inactivity, smoking, alcohol use, unsafe sex, urban air pollution, indoor use of solid fuels, and contaminated injections from healthcare settings. To evaluate exposure to risk factors and relative risk by age, sex, and region, the investigators analyzed data from the Comparative Risk Assessment project and from new sources, and applied population-attributable fractions (PAFs) for individual and multiple risk factors to site-specific cancer mortality provided by the World Health Organization. The contributions of factors to mortality for each cancer site were analyzed separately for high, middle and low income countries.

Of the 7 million cancer deaths considered, investigators estimated around 2.43 million might have been prevented. Further analysis of deaths showed that more than a third (37%) were from lung cancer, most of the deaths (1.76 million) happened in low and middle-income countries, and that men accounted for 1.6 million deaths, compared with 0.83 million for women.

Smoking, alcohol use, and low fruit and vegetable intakes were the leading risk factors for death from cancer worldwide, and for low and middle-income countries. In high-income countries, smoking, alcohol use, and weight problems (being overweight or obese) represented "the most important causes of cancer". In addition, sexual transmission of human papilloma virus was a leading risk factor for cervical cancer in women from low-and-middle-income countries.

Cervical cancer: increased risk after CIN treatment

Women treated for cervical intraepithelial neoplasia (CIN) remain at higher than average risk of developing cervical cancer in the 20 years following treatment, reports the BMJ (2005;**331**:1183–85).

Researchers from Helsinki University Central Hospital identified 7564 women treated for CIN between 1974 and 2001, and followed them through the Finnish Cancer Registry and Finnish Population Registry until 2003. The team compared the incidence of cervical and other cancers in their cohort with the incidences expected in the general population, presenting results as incidence ratios (ratio of observed to expected number of cases).

In the first decade following treatment, the incidence ratio was 2.7 (95% CI = 1.4–4.8). Risk peaked during the second decade after treatment (IR = 3.1; 95% CI = 1.5–5.7) then dropped off during the third decade (IR = 1.4; 95% CI = 0.04–8.0).

The women were also at increased risk for cancer of the vulva (IR = 4.1; 95% CI = 1.5–8.9), vagina (IR = 12.0; 95% CI = 3.9–28.0), lung or trachea (IR = 2.5; 95% CI = 1.9–3.5) anus (IR = 5.7; 95% CI = 1.2–17.0) and any cancer (IR = 1.3; 95% CI = 1.2–1.4).

Risk was higher for women with lower grade lesions (grades 1 and 2) than for those with grade 3. Grade 1 lesions were associated with an incidence ratio of 3.1 (95% CI = 1.4–6.2); grade 2 lesions were associated with a ratio of 3.7 (95% CI = 0.8–10.9); while grade 3 lesions had a ratio of 2.2 (95% CI = 0.5–6.4).

The authors speculate that the explanation may be that patients with lower grade lesions are not followed-up as systematically as patients with high grade lesions.

"The study shows that mild lesions have a similar or greater risk of developing cancer than more severe ones, and that these women should continue to be offered smears every 3–5 years for 20 years," said Dr Pekka Nieminen, the senior author, from Helsinki University Hospital, Finland.

The authors maintain, treatment of CIN is still effective and that an estimated 28–39% of cases without treatment would have progressed to invasive cancer.

They are now investigating whether treatment methods used correlate in any way with the later development of cervical and other cancers.

Transdermal fentanyl effective for children

Using transdermal patches to deliver the opioid fentanyl provides an effective way to control paediatric pain, reports an article published online in the journal *Cancer*, (November 14).

Dr Julia Finkel of the Children's National Medical Center (Washington, DC) investigated the safety and efficacy of transdermal fentanyl in 173 children already receiving oral and parenteral opioids to control moderate to severe pain due to malignant and non-malignant conditions. The 15 day single-arm, open-label trial showed average daily pain intensity levels, as reported by the children or their parents on a 10-point scale, decreased from 3.5 ± 0.23 at baseline to 2.6 ± 0.21 by day 16.

Results from global assessments of pain reduction, safety, and quality of life, conclude the investigators indicate transdermal fentanyl "is an acceptable alternative to oral opioid therapy in children." The approach, they add, is especially useful for controlling chronic pain in children with "life-limiting conditions in whom oral or injectable routes of delivery are difficult to administer or would add further distress."

Infertile men need investigation for testicular cancer

Men undergoing infertility treatment are over 20 times more likely to be diagnosed with testicular cancer than men in the general population , finds a study in the *Journal of Urology* (2005; **174**:1819–22). "Screening for testicular cancer could now become a standard part of all male infertility treatment," predicted Dr Marc Goldstein, the lead author from New York Presbyterian Cornell Medical Center.

For some time there has been evidence that infertility and testicular cancer have a common origin, going beyond the well known risk factor, cryptorchidism.

To investigate further, Dr Goldstein and colleagues undertook a retrospective review of the notes of 3847 men with infertility and abnormal sperm treated over 10 years at the centre. The investigation revealed 10 cases of testicular cancer. In comparison with similar aged men in the general population on the Surveillance, Epidemiology and End Results database, infertile men were found to have a 22.6 fold increased risk of testicular cancer.

The study showed that it would be necessary to screen only 500 infertile men to identify 1 case of testicular cancer, compared to breast cancer screening of 1500 women to pick up a single case.

- Survivors of testicular cancer have nearly twice the lifetime risk of developing additional forms of cancer compared to men who have never had testicular cancer, reports the *Journal of the National Cancer Institute* (2005;**97**:1354–65).

Dr Lois Travis and colleagues from the National Cancer Institute (NCI) in Bethesda, Maryland, identified 40,576 men who had survived at least 1 year after a diagnosis of testicular cancer from population based registries in North America and Europe.

Results showed that overall, the men had a risk 1.9 times that of men of comparable age who did not have testicular cancer. Risk was highest for men diagnosed in their 20s and lower for those diagnosed later in life. The most common second cancers were stomach, pancreas, bladder and connective tissue disease.

Although the authors believe the treatment of testicular cancer was the major cause of later cancers, the study could not prove it. Radiation, which most of the men received, is known to cause cancers, particularly in the area that is exposed to the radiation. Chemotherapy is generally thought to be a less likely cause of second cancers, but even men treated with only chemotherapy had a higher risk of getting new cancers. The authors conclude that more research is needed to find out if specific treatments (particular radiation doses or certain chemotherapy drugs) are more or less likely to increase the risk of secondary cancers.

Antibiotic link to NHL

Most medications have no effect on an individual's risk of non-Hodgkin's lymphoma (NHL), reports the *American Journal of Epidemiology* (2005; **162**:965–74), although the study did find elevated risks with high usage of antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs).

To investigate conflicting results from earlier studies over whether medications were associated with NHL, Dr Ellen Chang and colleagues from the Northern California Cancer Centre, Fremont, compared data on medications taken by 3055 subjects enrolled in the Scandinavian study, with 3187 healthy controls drawn from Danish and Swedish population registers.

The study showed people who had used antibiotics more than 10 times during adulthood were 1.8 times more likely to develop NHL than those who had never used antibiotics. In addition, a high cumulative dose of NSAIDs, such as ibuprofen, was associated with a slightly raised risk of developing lymphoma.

The authors, believe the apparent association is more likely due to repeated infections and/or susceptibility to infections treated with antibiotics, than the harmful effect of antibiotics themselves. Similarly, it is the underlying inflammation, rather than NSAIDs, that is likely to account for positive associations.

Study finds link between thyroid cancer and melanoma

People diagnosed with cutaneous melanoma are at increased risk of developing thyroid cancer, according to a study in the *Int J Cancer* (2006;**118:**185–8). The increased risk could be from a shared genetic mutation, as molecular studies have shown mutations in the *BRAF* gene in both cancers. This mutation creates a signal inside the cell that encourages the cell to continue dividing, says lead author Hensin Tsao (Massachusetts General Hospital, Boston, MA, USA). "It is possible that both the thyroid cell and the melanocyte share a vulnerability to an unidentified process that leads to *BRAF* mutations. Or, both cells are deficient in their ability to correct this type of *BRAF* mutation", he adds.

By use of the US National Cancer Institute's Surveillance, Epidemiology and End Result database, the investigators assessed 73,274 patients with cutaneous melanoma and 27,138 patients with thyroid cancer who were registered in the database between 1973 and 2000. Data analysis showed an increase of 2·17-times in risk of developing thyroid cancer after a diagnosis of cutaneous melanoma. The risk was slightly higher in men; for those diagnosed more recently; and during the first 3 years after diagnosis of cutaneous melanoma. The researchers also detected a much smaller increased risk of cutaneous melanoma in those who had survived thyroid cancer, which was of borderline significance. If the findings are replicated in other populations, prospective studies might be warranted to look for thyroid lesions in people who have survived melanoma. In the meantime, melanoma survivors should ask their doctors about symptoms of thyroid cancer, and thyroid cancer survivors should have a yearly skin check, Tsao advises.

Leslie Harris O'Hanlon

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Oncologists miss smoking-cessation opportunities

Despite the recognised importance of stopping smoking for all cancer patients, diagnosis is frequently missed as a "teachable moment" for smoking-cessation, concludes a literature review. The authors of the study, published in *Cancer* (online 28 November) found that up to one-third to one-half of cancer patients either continue to smoke after diagnosis or relapse after initial attempts to quit.

"A growing body of evidence indicates that continued smoking after a diagnosis of cancer has substantial adverse effects on treatment effectiveness, overall survival, risk of second primary malignancy and quality of life," write the authors Ellen Gritz and colleagues, from The Anderson Cancer Centre (Houston, Texas), adding adverse effects are found for both patients with smoking related cancers and those with non-smoking related cancers.

The literature review identified that continuing to smoke after a diagnosis of cancer is associated with the following problems:

- A negative effect on overall survival in patients with lung, head and neck, prostate and cervical cancers.
- Increased risk of developing second primary malignancies.
- Lower rates of complete response to radiation therapy.
- Exacerbated oral mucositis, loss of taste, xerostomia, weight loss, and fatigue.
- Since smoking increases the hepatic metabolism of many drugs, continued smoking may decrease the therapeutic effectiveness of chemotherapy and other medications.
- After surgery increased risk of wound infection and detrimental effects on wound healing.
- Lower QOL scores.

"Although more research is clearly needed to empirically test smoking-cessation interventions with cancer patients, encouraging results have been demonstrated with brief physician delivered advice and nurse-delivered hospital cessation programs," wrote the authors, recommending oncologists inquire about and document patient's smoking history at the initial consultation.

They recognize unique disease-related issues need to be taken into consideration for cancer patients. It is important, for example, to offer specially tailored suggestions for exercise and dietary change. There are also medical contraindications to certain types of nicotine replacement therapy, for example, people with oral cancers may be unable to use oral forms of nicotine replacement.

The study concludes that further research is needed to test smoking-cessation interventions for cancer patients and to determine individual barriers to quitting among this group.

- A new experimental smoking-cessation treatment, varenicline, improves the odds of smokers quitting, reported two studies presented at the American Heart Association meeting (Dallas, Texas, November 13–16).

In the two double-blind placebo-controlled studies, involving about 2000 smokers, participants received either varenicline, bupropion, or placebo for 12 weeks. Patients were followed for an additional 40 weeks without treatment.

In both studies, 44% of varenicline-treated patients quit by the end of the 12-week treatment compared to 30% taking Zyban and 18% taking placebo. But after a year, 1 study showed 22% of patients taking varenicline remained smoke free, compared with 16% in the bupropion group, a result that did not reach statistical significance.

Varenicline represents the first selective nicotinic acetylcholine receptor partial agonists smoking session therapy. In November Pfizer submitted a New Drug Application to the FDA for varenicline and applied for European registration.

Radiation therapy increases hip fractures

Women over 65 who undergo radiation therapy for pelvic malignancies are at increased risk from pelvic fractures, reports *JAMA* (2005;**294**:2587–93).

Nancy Baxter and colleagues from the University of Minnesota, Minneapolis, reviewed cancer registry data on more than 6400 women aged 65 and older, who had been diagnosed with pelvic malignances (anal, cervical or rectal cancers) between 1986 and 1999. They then compared the medicare claims of the 2855 women who underwent radiation therapy with the 3537 women who did not.

The investigators found that for women who had undergone radiation therapy for anal cancer 14% had experienced a pelvic fracture over 5 years, compared to 7.5% of women who did not receive radiation. For cervical cancer the numbers were 8.2% and 5.9%, respectively, and for colon cancer 11.2% versus 8.7%. Almost all of the fractures (90%) were hip fractures. The researchers found no significant difference in the rate of arm and spine fractures between women who received pelvic radiation therapy and those who did not.

"Admittedly, the technology used today and the way radiation therapy is given has improved and is better controlled than in the 1980s and 1990s," Dr Baxter said. "Nonetheless, our findings point out a concern that women who undergo radiation therapy for pelvic malignancies and their physicians need to be aware of and take precautions to prevent fractures."

She added that the study looked only at older women, so the findings cannot necessarily be extrapolated to other populations, such as men or younger women.

Gene markers lead to more precise treatments

Loss of specific genes on chromosome 1 or 11 are associated with an increased risk of mortality in children with neuroblastoma, reports the *NEJM (2005;**353**: 2243–53)*.

John Maris and colleagues from the Children's Hospital of Philadelphia studied 915 children with neuroblastoma and found that a loss of heterozygosity at unbalanced 11q and 1p36 areas of the genome was associated with worse outcomes ($P < 0.001$).

The team believe adding these markers to the currently used prognostic variables would allow more precise treatment recommendations. "Because both 1p and unb11q LOH are independently predictive of worse progression-free survival in patients with low-risk and intermediate-risk disease, the Children's Oncology Group plans to use these markers to assign the number of cycles of adjuvant chemotherapy in the hope of averting a relapse of disease," they write, adding that the approach would also have the advantage of not subjecting children with lower-risk cancer to over treatment.

PODIUM

Avoiding reinvention of the wheel

Jim Cassidy – Cancer Research UK professor of Oncology at the Beatson Oncology Centre, Glasgow – developed an interest in the financial impact of new drugs as a result of working in drug development. Here, he cautions that with so many new drugs in the pipeline, oncology therapies are reaching the limit of affordability. Professor Cassidy, who specialises in GI cancer, outlines the innovative approach he is spear heading, where new drugs are assessed for cost-effectiveness at the same time as being considered for efficacy.

Professor Jim Cassidy

Could you summarise the current financial crisis facing oncology drug development?

Over the last 10 years a number of new anti cancer drugs have been developed and it's becoming increasingly clear these drugs are reaching the limit of affordability. Unless we urgently address such issues we'll end up in the situation where new drugs will only be available to those who can afford them. One scenario (already seen with Herceptin® in the UK) is that people will re mortgage their homes, but the more likely outcome is that many simply won't have access to new drugs, jeopardising the entire concept of socialised health care in Europe.

What level of evidence is needed for new drugs to be available?

If you can show in 2 high quality randomised control phase III trials that an intervention is beneficial in comparison to the standard of care, then from the clinical point of view this provides enough evidence. You can't specify size limitations for oncology trials since when dealing with rare tumours it'd be difficult to recruit enough subjects. The situation proves more complex when 2 trials point in opposite directions. Here more trials are needed or a decision to go no further.

How much of a role should economics play?

The science of pharmaco economics is still in its relative infancy, with many different models in use. The current situation is that companies use 1 economic model in drug submissions and then NICE uses a totally different model for evaluations. To add to the confusion, different NICE panels often use different models for individual evaluations. What's needed is for ground rules to be introduced early in the licensing process, so everyone knows whether a drug is economically viable and should be promoted for use.

How can better economic models be developed and who's responsible?

Academics and pharmaceutical companies need to collaborate, with input from the regulatory authorities, to develop better economic models. What's needed is a body with a similar role to NICE in the UK, but with the ability to assess cost-effectiveness across Europe and provide a rating. This would be undertaken at the same time as efficacy is considered. Currently the result of having no such central organisation is that drugs have different rates of uptake across Europe leading to major inequalities, as highlighted in a recent report by the Karolinska Institutet.

Who should pay for economic research?

At the end of the day pharmaceutical companies have the responsibility to show if their products are cost-effective. It's important that a European regulatory authority is established to develop frameworks with clear processes for them to follow. You need an organisation that can step back and take a view as to whether the drug would be cost-effective. Ultimately, pharmaceutical companies would welcome the approach because it would save them from having to keep on re inventing the wheel by proving a product is economically viable in each individual country.

What are the challenges in developing such systems?

There are technical differences across the different European countries, such as how much oncology health care is delivered as an in patient and how much as an outpatient. It should be possible to devise formulas where costs can be calculated for different scenarios. But we're up against a culture where if research isn't done in a particular country it gets repeated.

With limited budgets how do we rank the relative merits of the new cancer therapies against treatments for other chronic conditions?

Ranking which intervention has greater social importance is controversial. The difficulty is that people's views are very personal – if you've cancer you'll put that at the top of your list, but for diabetics priorities are entirely different. It's here the QUALY system provides a good starting point for discussions. In Cancer, difficult decisions need to be made about whether you concentrate limited resources on curative treatments or spread the budget to include end of life and palliative care. Ultimately, you'd hope to achieve a balance so both are funded.

Do we need to change our attitudes towards the pharmaceutical industry?

There's a tendency among certain oncologists to class drug companies as the devil incarnate, who's only out for profits. But with this comes a failure to appreciate that without drug companies we'd never be able to develop new drugs, since no government would risk that amount of investment. Governments need to introduce incentives that enable drug companies to reduce development costs. Fiscal measures might be brought to bear to alter taxation systems, and there are also other innovative schemes, where financial risk is shared between the provider and supplier. We all need to start working with the pharmaceutical industry towards the common aim of reducing drug costs for our patients.

Who should be raising these issues?

We're hoping a supplement we're preparing for EJC on pharmaco economics, scheduled for publication later this year, will get these issues into the public arena for debate. The supplement will consider economics from both the European and International perspective, and encourage oncologists to call for regulatory change.