Beyond the Herceptin hype...

We need to raise the level of debate

Anna Wagstaff

Herceptin may turn out to be the biggest advance in treating breast cancer since tamoxifen. But if we are to prevent soaring drugs bills eating up our health budgets or barring Europe's poorer patients from the latest therapies, cancer professionals will have to wrest back the debate from the unfettered hype of the mass media.

For months, the British press has been reporting stories of women with breast cancer spending their life savings, putting their houses on the market, flying to India, marching on the Prime Minister, or heading for the European Court of Human Rights, to get their hands on the latest "wonder drug". Herceptin (trastuzumab), a monoclonal antibody that targets the HER2 receptor, has been approved for more than six years for use in breast cancer for patients who over-express the HER2 protein (HER2+ patients) and who have metastases. However, the women at the centre of the current media storm are all early breast cancer patients, and an application has only just been submitted for approval in this setting.

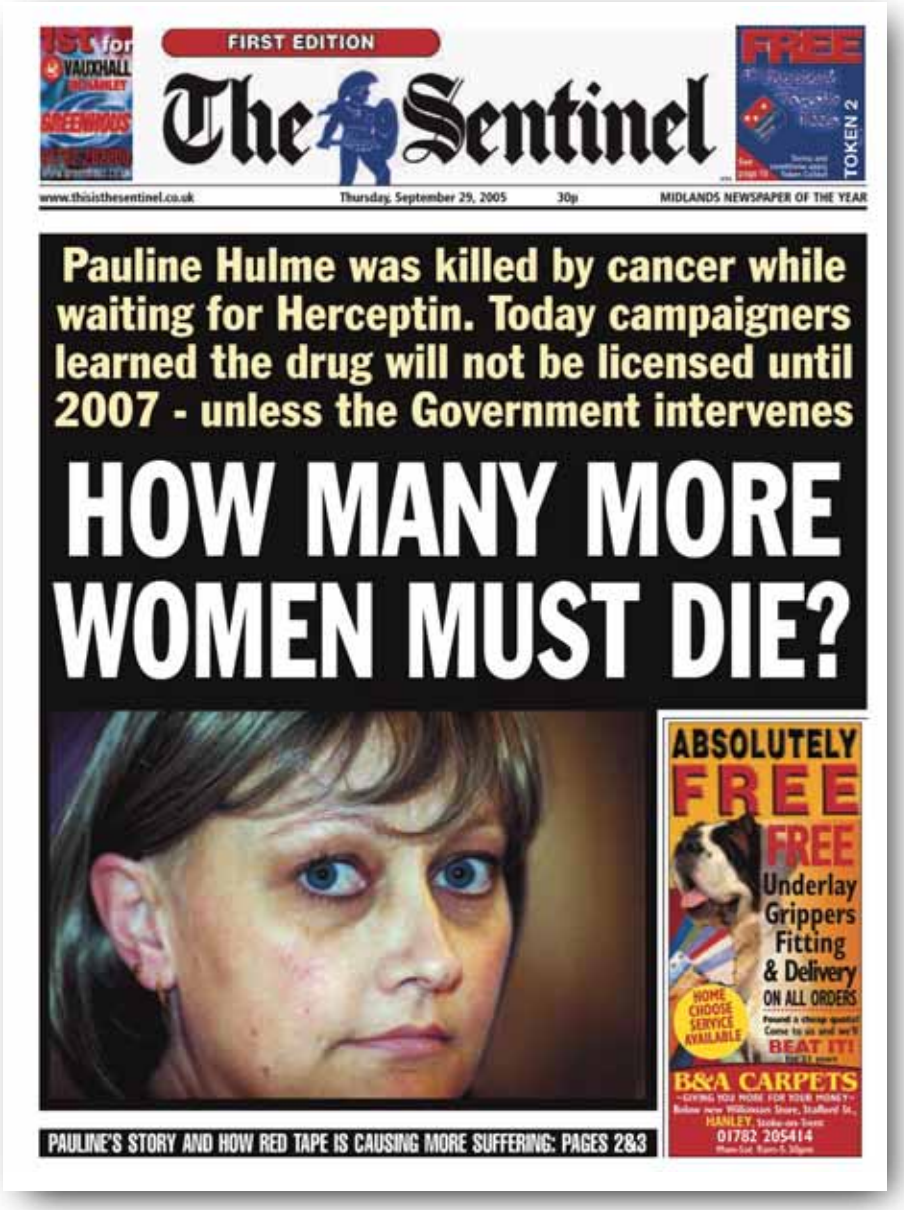
For patients going through aggressive chemo- and radiotherapy while fighting for access to the drug, each story represents a traumatic personal experience. For the media, a cocktail of righteous indignation, alarmist headlines and human interest guarantees increased sales, especially when younger women and children are involved.

In September 2005, Sky News (UK) highlighted the story of Barbara Clarke, who was being denied Herceptin by her local National Health Service care provider (primary care trust or PCT). The 42-year-old former nurse, foster mother to an 11-year-old boy with a life-limiting disease, was threatening to take her case to the European Court of Human Rights. Her story was subsequently picked up and run throughout the national press. Her PCT reversed its decision on the grounds of "exceptional circumstances".

In the Midlands town of North Stoke, a group of HER2+ patients banded together as Women Fighting for Herceptin. Their local paper plunged into battle on their behalf. "This was something we felt the local community would have instant sympathy with. It was a fantastic local story," said the editor, in a recent BBC documentary. "We splashed the front page day after day. We put a reporter on the story full time. We gave it a huge amount of pagination."

A string of stories kept the drug in the news, but did little to help thousands of women diagnosed with HER2+ early breast cancer to understand their own chances of survival.

There are no established risk figures for the population covered by adjuvant Herceptin trials – HER2+ patients with early breast cancer. But, even on conservative estimates, breast cancer as a whole now has a survival rate of around 70% averaged


FIRST EDITION

The Sentinel

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FREE TOKEN 2

Pauline Hulme was killed by cancer while waiting for Herceptin. Today campaigners learned the drug will not be licensed until 2007 - unless the Government intervenes

HOW MANY MORE WOMEN MUST DIE?

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PAULINE'S STORY AND HOW RED TAPE IS CAUSING MORE SUFFERING: PAGES 2&3

A powerful campaign led by women desperate to improve their chances forced politicians' hands

over all types and stages of breast cancer. Within that overall figure, HER2+ breast cancers are particularly aggressive. They are estimated to have a risk of relapse about 1.5 times that of non-HER2+ tumours that have similar characteristics (e.g. nodal and hormonal status).

Though no woman wants to live with odds like these, the media certainly hyped the threat well out of proportion. Early breast cancer was often confused with metastatic cancer. The finding that Herceptin can halve the relative risk of a recurrence was sometimes interpreted to mean that the drug offers patients a one in two chance of survival. Figures such as an 84% risk of dying from the disease were routinely quoted.

Little wonder that one woman told the High Court: "I feel the refusal of Herceptin is as though I have been given a punishment like a death sentence. With my prognosis, waiting for the cancer to return is like waiting on death row."

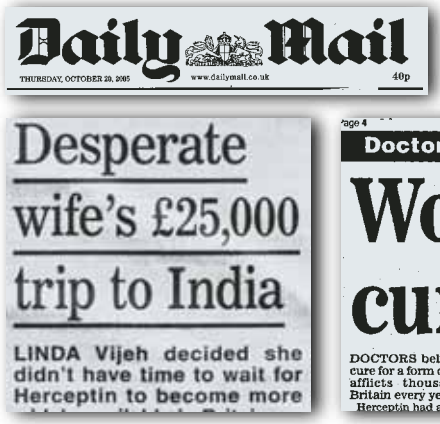
Women who won their battle to secure the drug also tended to overstate the level of protection. One said, "I feel as if my life has been saved…I can sit back and relax."

As one story followed the next, Herceptin took on a mythical status. Media stories of women stampeding to gain access to a life-saving drug became a self-fulfilling prophecy, as it was hard for even the most sceptical and level-headed to think about risk objectively. Some women apparently now believe that it is preferable to have a HER2+ cancer, in order to gain access to Herceptin.

As demand for the drug soared, oncologists found themselves squeezed between patients desperate for the drug and cash-strapped PCTs, who were unwilling to pay £30,000 (43,500 euros) to fund the drug for one woman for one year. Some oncologists also felt ill-equipped to make a judgement on the basis of the available evidence about risk and benefit.

Reacting to the media campaign, the British Secretary of State for Health put pressure on PCTs, saying that cost alone should not be a reason for refusal. Despite being £7 mn (10.2 mn euros) overspent and receiving no additional resources, North Stoke PCT felt compelled to reallocate its spending priorities in favour of Herceptin.

The British system for ensuring best use of limited health funds – often held up as a model for the rest of Europe – had been blown out of the water. The health policy think-tank, the King's Fund, accused the Secretary of State of "putting pressure on providers to use an unlicensed drug". The British Association of Pharmaceutical Industries accused her of sending out mixed signals about drugs regulation. "The Secretary of State wants everybody to have a drug that we don't really know works or not."


Daily Mail
THURSDAY, OCTOBER 20, 2005 www.dailymail.co.uk 40p

Desperate wife's £25,000 trip to India

LINDA Vijeh decided she didn't have time to wait for Herceptin to become more

Page 4

Doctors hail Herceptin after study shows it halves the r

Wonder drug 'could cure breast cancer'

DOCTORS believe they may have a cure for a form of breast cancer which afflicts thousands of women in Britain every year.
Herceptin had already been unveiled as

By Julie Wheldon
Science Correspondent

cure. They spoke of 'stunning' and 'revolutionary' results after scrutinising the full data of a study of thousands of women with early

particularly aggressive tumours. The study of more than 5,000 patients in 39 countries found there were 220 recurrences of cancer in those who did not receive Herceptin, compared to 127 among those on the drug for a year - a reduction of 46 per cent.

Voices of protest asked what this would mean for patients less able to catch the media eye – for geriatric care, mental health services, or rarer cancers.

Questions were raised about how researchers, clinicians and regulators had allowed themselves to become so sidelined.

Revolution or evolution?

If the interplay between the mass media and patient campaigners heightened a sense of crisis, cancer researchers and academic journals also played a role.

The preliminary results of three adjuvant Herceptin trials in early breast cancer published in the *New England Journal of Medicine* (20 October 2005) were accompanied by a glowing editorial by Gabriel Hortobagyi. He described the results as "simply stunning" and said that they suggested "a dramatic and perhaps permanent perturbation of the natural history of the disease, maybe even a cure". The results were "not evolutionary but revolutionary".

The mass media might have problems with 'perturbation', but they understand the word 'cure'. One of Britain's most popular daily papers, the *Daily Mail*, ran the story under the title: Wonder Drug 'Could Cure Breast Cancer'. "Doctors believe they may have a cure for a form of breast cancer which afflicts thousands of women in Britain every year…"

They also quoted JoAnne Zujewski, head of breast cancer therapeutics at the US National Cancer Institute, as saying, "In 1991, I didn't know that we would cure breast cancer, and in 2005, I'm convinced we have."

Richard Horton, editor of the *Lancet*, says that senior cancer researchers should ask themselves how they could draw such conclusions on the basis of the results of these three trials. In an editorial, he pointed out that the results were from interim efficacy analyses, and none of the trials had run their full intended course. (The trials had been stopped early because the preliminary results were so good.) Horton said that some crucial data on side-effects were missing, while two of the three trials had been combined for the purposes of the study, "which may reflect the expectation that neither trial alone would demonstrate a positive result."

"The best that can be said about Herceptin's efficacy and safety for the treatment of early breast cancer," said Horton, "is that the available evidence is insufficient to make reliable judgements. It is profoundly misleading to suggest, even rhetorically, that the published data may be indicative of a cure for breast cancer."

"Naturally," said Horton, "[Hortobagyi's] comment was picked up and repeated across the world, fuelling demand for rapid access to Herceptin."

What the trials say

At the time the results were published, the median follow-up in the HERA trial, which was run by the Breast International Group and forms the basis for Roche's application for approval, was just over one year. In the combined study of the two North American trials reported in the same issue of the NEJM – the NSABBP (National Surgical Adjuvant Breast and Bowel Project) trial B-31 and the NCCTG (North Central Cancer Treatment Group) trial N9831 – the median follow-up was just two years.

That leaves a lot of room for interpretation. Those lining up behind the 'stunning' and 'revolutionary' interpretations point to very impressive figures for disease-free survival, which show the relative risk of relapse (local, distant, contralateral or second primary) halving in all three trials, and continuing beyond

What would this mean for patients less able to catch the media eye?

the two-year 'hump' at which the majority of relapses tend to occur. Supporters point out that this drug was designed to intervene in a mechanism identified as probably driving the disease, and that the results are consistent with hitting the mark.

Those calling for a more cautious approach argue that interim data can prove misleading, adjuvant drugs have to prove themselves over a longer time-scale and the data on overall survival is statistically very weak. They also point out that, given the drug's cardiotoxicity, more data are needed on long-term side-effects. These risks are especially important because adjuvant drugs are inevitably given to a proportion of patients who would not have relapsed anyway.

The results of two additional trials into adjuvant Herceptin were presented at the San Antonio Breast Cancer Symposium, in December 2005. These were the BCIRG (Breast Cancer International Research Group) trial, and the FINHER trial, carried out by a team at the Helsinki Central Hospital in Finland. The latter, although very small, is intriguing, because it looked at the effects of Herceptin given for just nine weeks, rather than for one year as in the other studies.

The results of the trials, including the cardiac effects, median follow-up and numbers of patients, are shown on pages 20,21. The trials show that taking Herceptin reduced the relative risk of a relapse by around half, with hazard ratios ranging from 0.61 to 0.48 in the larger trials and 0.46 in the smaller, but longer, FINHER study. The absolute risk of any patient on the trial relapsing was reduced by somewhere between 3 and 12 percentage points in the larger studies. This reduction in absolute risk of relapse increases with length of follow-up, reaching 18 percentage points at four-years in the North American trials. However, these figures have to be treated with caution, because not many patients had been followed-up for four years.

Figures for overall survival suggest that the relative risk of dying was reduced by between 22% and 44% if you were on Herceptin, but in all cases the absolute numbers were too low for the results to reach statistical significance. This does not mean halving the absolute risk of dying – because many patients were already surviving without Herceptin.

So what about side effects? The data on cardiac toxicity show a greater-than-10% decline in left ventricular function (LVEF) in 7%–17% of patients on Herceptin. The higher figure relates to patients on the more aggressive of the BCIRG regimens, in which the trial authors also noted a statistically significant higher incidence of "asymptomatic and persistent" LVEF decline. No LVEF data were given for the North American trials, but they did report that grade 3 or 4 congestive heart failure increased by around 3 percentage points.

Despite these risks and the short follow-up time, some leading researchers feel that the *Lancet* criticisms are overstated. Fatima Cardoso, from the Jules Bordet in Brussels, a clinician and researcher specialising in HER2+ breast cancer, says, "We have four trials with a very large number of patients in total, all with very consistent results. Even if half the benefits disappeared with longer follow-up – which no-one is predicting – they would still be astonishing. The only drug that gives similar results in terms of size of effect is tamoxifen.

"We've had to wait 30 years to see these kinds of results again."

Though comparison with tamoxifen has also been made by others, tamoxifen can be used in about two-thirds of breast cancers (hormonal-dependent cancers) whereas Herceptin is directed at the fewer than one in four breast cancers that are HER2+. However, Cardoso points out that HER2+ breast cancers are among the most aggressive "[Herceptin] has a huge impact because it works for a group with one of the worst prognoses."

She also argues that we already know a great deal about the side-effects of Herceptin, as the drug has been used in a metastatic setting in thousands of women over a period of seven years.

Cardoso believes that the *Lancet* editorial derailed delicate negotiations in many countries about access to the drug. Although she says it was "certainly not" right to talk about a cure, she defends Hortobagyi's use of 'stunning' and 'revolutionary'.

"When we compared anthracyclines with no anthracyclines we saw a benefit on average of about 5%. When we compare taxanes with no

CLARE LEWIS / STOKE SENTINEL

Alison Poole outside the Prime Minister's residence, 10 Downing Street, where Women Fighting for Herceptin delivered a 35,000 signature petition last September

taxanes, again we saw a benefit on average of about 5%. And now we see a benefit of 50% reduction in relapse and about 20–30% reduction in deaths. It's a huge difference."

Cardoso wants to see every patient tested for HER2, and Herceptin brought into widespread use in the adjuvant setting as soon as possible. "Herceptin should be a priority drug to approve in any country that can afford it."

However, Richard Horton, from the *Lancet*, says that the HERA and North American studies gave only interim data, and had not achieved sufficient primary endpoints to give statistically reliable information.

He argues that data gained about side-effects when using a drug in metastatic cancer cannot simply be transferred to the adjuvant setting. He takes issue with combining results from two North American trials in a single analysis, and drawing conclusions from four or five separate trials in the absence of a proper meta-analysis.

"That's a situation in which nobody can make a rational judgement about the balance of risk and benefit in a woman specifically with early breast cancer.

"The history of medicine is littered with wonderful early results which over a period of time turn out to be not so wonderful – or in fact even adverse. If you look at hormone replacement therapy, or Vioxx [rofecoxib]… there are a whole string of recent examples where preliminary data led to a lot of excitement and caused changes in clinical practice, and then eventually we realised they had done more harm than good.

"Why is it we never learn these lessons? We seem condemned to make the same mistakes each time with any new drug. It may be that Herceptin is the best news for women with breast cancer for a generation, but we just don't know that for sure yet….I can't see for the life of me why that statement is controversial. It seems to me just good clinical practice."

Pinuccia Valagussa, head of the operations office for clinical trials at the Istituto Tumori in Milan, which took part in the HERA trial, says that the short time frame may not be a problem. She has been following up patients involved in the trials of the first adjuvant chemotherapy, CMF (cyclophosphamide, methotrexate and fluorouracil), for 30 years, and has criticised an increasing trend towards publishing trial results too early. But not in this case.

Her experience with CMF makes her believe that efficacy at an early stage will be maintained. "At the time [of the CMF trial] we could see there were subsets of patients who benefited, and this has been maintained for 30 years. There is no reason why that should not happen with Herceptin."

Jonas Bergh, a breast cancer specialist at Stockholm's Karolinska hospital, also believes that the evidence from these trials was overwhelming. Having served as an external advisor to regulatory bodies, he is naturally cautious and acknowledges the concern about lack of long-term data on side-effects. However, in this case, "the data are of such magnitude that you cannot ignore them."

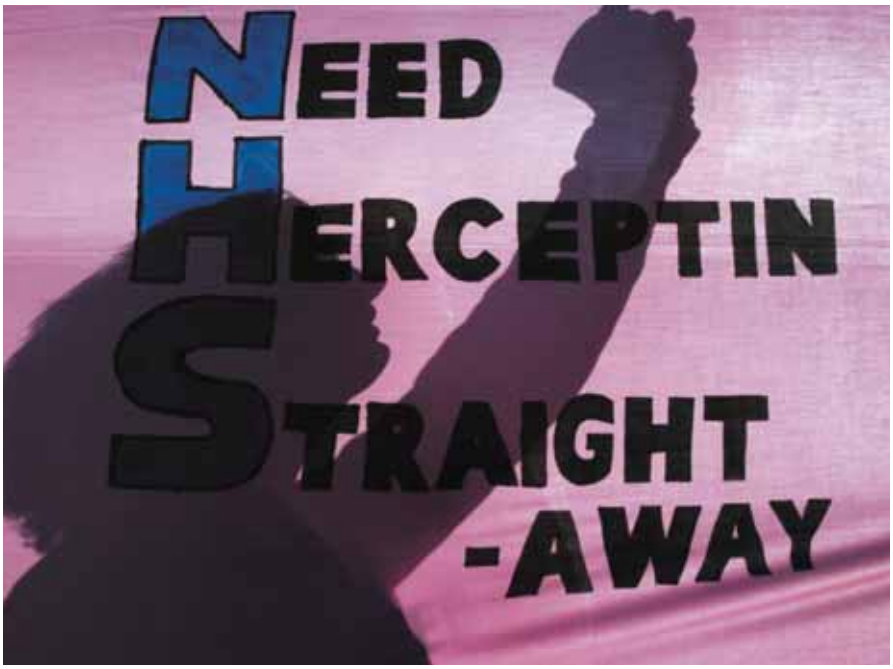
He believes excessive caution can delay advances, and cites earlier doubts about adjuvant chemotherapy and misplaced concern in a large part of Europe that it should not be given to young women, because of possible long-term side-effects.

"I personally think that the data are impressive, although the world 'revolutionary' may be too strong."

Bergh argues that on the basis of what is now known, all primary breast cancers should now be tested for HER2, not least because it may

"It is profoundly misleading to suggest… that the published data may be indicative of a cure"

"We've had to wait 30 years to see these kinds of results again"



CLARE LEWIS / STOKE SENTINEL

have implications for the selection of chemotherapy and for the use of conventional endocrine therapies. "Personally, I think it is reasonable to offer patients the option of adjuvant Herceptin if they are shown the data, including the data on risk of possible side effects." The Swedish Breast Cancer Group is already recommending this approach.

As someone with a regulatory interest, Bergh agrees that lack of longer-term data is a problem for patients and oncologists who have to make a decision now, but he says there was no ethical option to ending the trials early.

The problem, he says, is a byproduct of the degree of international coordination which allows much faster accrual to clinical trials, compared for instance to the days of the tamoxifen trials, which took far longer to reach a conclusion.

One option, he suggests, might have been to design the studies on a much smaller scale. It would then have taken longer to show that magnitude of effect. The extra time would have given stronger survival data and more information about long-term side-effects. However, says Bergh, the biological observations in terms of time to recurrence would still have been similar, "And the downside with that type of study is that people would have said: it is only one small study, we have to repeat it. And then we are talking many more years before we would have known the results."

He says that regulatory authorities increasingly accept disease-free survival, as used in the Herceptin trials, as a surrogate for overall survival, particularly with non-cytotoxic drugs, which usually carry a lower level of risk.

As for the problem short trials present for reliable data on side-effects, EMEA has tried to address this by placing greater emphasis on vigilance in reporting side-effects quickly once the drug is on the market.

A LOST GENERATION

Arguably, the time patients have to wait for a new drug to complete the regulatory process creates as great a problem as difficulties posed by the very short timescales of the trials.

Alison Poole, one of the Women Fighting for Herceptin, describes herself as "One of the lost generation of mothers, daughters and sisters… too late for the trial, but too early for licensing…. Our argument was, what happens to ladies like myself who could benefit from Herceptin, but we can't get it on the trial any more? We've got to wait and wait for it to be licensed. And we know that HER2 is very aggressive, and it is more likely to come back sooner rather than later. So we didn't feel as if we had time to wait."

Pressure to speed up the time taken to approve new drugs or new drug indications has been building over the past few years. Roche, manufacturer of Herceptin, has been among the chief critics, and funded the Karolinska report last year which highlighted disparities in access time

to new drugs in different countries. Ironically, with Herceptin the initial delay was due to Roche itself, which took almost eight months from the first announcement of the trial results, at ASCO last May, to submit an application to EMEA (though they claim this is their quickest time ever).

One answer to the dilemma of risks and access may lie in finding better procedures to allow patients at risk access to experimental drugs or indications while they are going through the approvals process, based on clear criteria.

A variety of approaches to this problem, has led to a wide variation in pre-approval access across Europe (see p23). Patients in Greece, Spain, Germany and Belgium are largely denied access (unless they pay themselves), while those in France, Sweden, Italy and Ireland have access, at least on an individual basis.

In the majority of countries, physicians have the right to prescribe drugs off-label (i.e. for a non-approved indication). Policies on funding, however, vary greatly. In the UK, prior to approval, it is up to the primary care trusts to decide whether to provide funding. With enormous pressure on resources, and in the absence of extra funding, many have argued that there is insufficient evidence either on the balance of risk and benefit or on whether the benefit is great enough to justify diverting funds.

These PCTs are trying to make evidence-based decisions and must think about the impact of making cuts elsewhere to fund a new drug. But this has proved hard to do in the face of a media frenzy and reactive politicians.

The BBC uncovered an e-mail sent by North Stoke to a neighbouring PCT, saying plaintively, "What a dreadful mess this all is. We've behaved properly and been thorough in our analysis, yet we get pressured into changing our minds to satisfy the whim of the PM [Prime Minister] and SoS [Secretary of State].

"The way is now open for single-issue groups to proliferate, and who will speak up for the disadvantaged – the mentally ill and those with learning disabilities?"

One suggestion is a central contingency fund to support patients between the closing of a trial and the licensing of the drug. This suggestion has also been floated to resolve similar problems in other countries, such as Sweden. One argument against is that it would tie up funds that are desperately needed elsewhere.

Others have suggested the need for a compassionate use scheme, negotiated between the manufacturer and individual health services to allow patients with life-threatening conditions free early access to drugs, if there are no alternative drugs available.

David Millson, visiting professor of medicines management at Keele University, UK, says that fully informed patients identified by oncologists as meeting the pivotal criteria could be offered treatment under such a scheme as an open arm of a phase III study. In a letter to the *Lancet* he writes, "Thus the patient with exceptional medical needs gains

THE ADJUVANT HERCEPTIN TRIALS

Trial	No. of patients/ median follow-up	Protocol	HR for DFS event
HERA[a] trial	3387 pts/ 12 months	H for 52 weeks vs no H in patients after locoregional therapy and min of 4 courses of any standard chemotherapy regimen	0.54 (95%CI 0.43–0.67) *P*<0.0001
NSABBP B-31	2043 pts/ 2.4 years	A+C➜P vs same regimen +52 weeks of H starting the same day as P	0.48 (95%CI 0.39–0.59) *P*<0.0001
NCCTG[a] N9831	1633 pts/ 1.5 years	A+C➜P vs same regimen followed by 52 weeks of H starting at the same time as P	
BCIRG	3222 pts/23 months	3 arms. (i) A+C➜T vs (ii) A+C ➜T+ 52 weeks of H vs (iii) T+Carbo +52 weeks of H	(i) vs (ii) 0.49 *P*<0.0001 (i) vs (iii) 0.61 *P*<0.0002
FINHER	231 HER2+ pts/ 38 months	2 levels of randomisation: (i) *All patients:* T vs V, each followed by C+E+5FU (ii) *HER2+ patients:* no H vs 9 weekly cycles of H concomitant with the T or V	0.46 RFS *P*= 0.0078; 0.43 DDFS *P*=0.0078

H - trastuzumab, A - doxorubicin, C - cyclophosphamide, P - paclitaxel, Carbo - carboplatin, E - epirubicin, 5FU - fluorouracil, T - docetaxel, V - vinorelbine, HR- hazard ratio, DFS - disease-free survival, CI - confidence interval, RFS - recurrence-free survival, DDFS - distant disease-free survival, LVEF - left ventricular function

access to an unlicensed medication under strictly controlled conditions. The NHS can access new medicines at 'no direct cost' until such time as the product is approved for marketing. The pharmaceutical company (by forgoing immediate financial gain) acquires valuable safety and efficacy data along with the goodwill of patients and health care providers."

He contrasts such scheme with "ad hoc patient treatment driven by political pressure, patient advocacy groups and media hype, with no prospect of obtaining useful data with which to further clarify the benefits of life-saving treatments."

His solution is also favoured by Cardoso. "I think Roche has a responsibility towards patients. They had the opportunity to quickly validate their drug in the adjuvant setting through international cooperation of all these investigators and all these patients, and will make a huge profit from Herceptin in early breast cancer. They have a moral responsibility to set up compassionate programmes in every country until the drug is approved. The burden should not be only on the shoulders of public health systems."

Responsibility for defending the regulatory process, however, belongs to everybody: researchers, manufacturers, patients, oncologists, funders and politicians, and it may be time for all of these groups to get round a table and talk about how things could be made to work better.

THE END OF SOCIAL HEALTHCARE?

Sadly, Herceptin has the potential to strain far more than regulatory procedures. At a cost of 43,500 euros for a one-year course, it presents a problem for any health service. Some commentators are predicting that Herceptin and the raft of designer drugs that will follow could spell the end for Europe's tradition of social healthcare.

Karol Sikora, Professor of Cancer at London's Imperial College School of Medicine, cites estimates that you need to treat around 18 patients in

Absolute DFS benefit	Overall survival	Cardiac toxicity >10% decline in LVEF	Severe cardiac events
8.4 percentage points (at 2 yrs)	37 vs 29 deaths 22% reduction in risk of death (ns)	2.21% vs 7.08% *P*<0.001	0 vs 0.54% *P*= 0.002
11.8 (18.2[b]) percentage points (at 3 (4) yrs)	92 vs 62 deaths; 33% reduction in risk of death HR 0.67, 95%CI 0.48–0.93; *P*=0.015 (ns)		0.8% vs 4.1% 0 vs 2.9%
(i) vs (ii) 9 (11[b]) percentage points; (i) vs (iii) 3 (7[b]) percentage points (at 3 (4) yrs)	(i) vs (ii) 36 vs 20 deaths 44% reduction in risk of death; (i) vs (iii) 36 vs 28 deaths 22% reduction in risk of death	(i) 9%, (ii) 17.3%[c], (iii) 8% (i) vs (ii) *P*=0.002; (ii) vs (iii) *P*<0.0001, (i) vs (iii) *P*=0.493	(i) 0.86% (ii) 2.62% (iii) 1.04%
13 percentage points (for both RFS and DDFS)	14 vs 6 deaths; 57% reduction in risk of death HR 0.43, *P*=0.08 (ns)	H (9 weeks) was not associated with any decrease in LVEF	0

a Figures for a third arm were excluded from the study; b Few patients were followed up this long; c A statistically significant higher incidence of asymptomatic and persistent LVEF declines (>550 days at last follow-up) was noted in (ii)

Sources: NEJM 2005, 335:1659-1672; 1673-1684 (HERA, NSABBP, NCCTG); www.bcirg.org (BCIRG) and www.sabcs.org (FINHER – see 2006 abstracts, Joensuu et al)

"What happens to ladies who could benefit from Herceptin, but can't get it on the trial any more?"

PETER MCINTYRE

Designer drugs carry a hefty price tag. Will Europe's stretched health budgets be able to cope?

order to prevent one death.

This is because, given in the adjuvant setting, there will be a proportion of patients who would not have relapsed anyway, and a further proportion for whom the standard chemotherapy regimen would have been sufficient, on top of which, the drug is effective in only half of the target group. Sikora's estimate corresponds to a figure reportedly circulating among UK primary care trusts of a £450,000 (660,000 euros) Herceptin drug bill to save a single life, and explains their reluctance to go down that road.

An economic analysis at the University of Ghent estimated that 750 women a year in Belgium alone would be eligible for adjuvant treatment with Herceptin, at a total cost (for the drug alone) of around 25.5 mn euros. Factor that up to the whole of Europe, where 245,000 women are diagnosed with breast cancer every year, 27,500 of them eligible for adjuvant Herceptin (stage II/III HER2+), and the annual bill for Herceptin would reach a whopping 950 mn euros. If its use were to be extended to stage 1 cancers, this would roughly double.

The Belgian analysis compared the cost of Herceptin in early breast cancer to a standard FEC (5-fluorouracil, epirubicin and cyclophosphamide) regimen, including the additional costs of cardiac monitoring and other related costs. It drew up cost-benefit graphs setting the additional cost of Herceptin against the benefits of additional (quality-adjusted) years of life and the future treatment savings from averting metastatic cancers. The team 'estimated' a value of a quality-adjusted extra year of life for a woman with breast cancer as 50,000 euros (roughly the price that Europeans are prepared to see spent from the public purse or insurance schemes).

The authors concluded that Herceptin could be cost-effective if health improvements are large enough and/or price discounts are given. However, they point out that even if the cost-benefit ratio is acceptable, it may still not be economically viable. Healthcare authorities will have to bargain hard over the price and may have to de-list older, less cost-effective treatments.

There is clearly scope to bargain. The Belgian study quoted the price of Herceptin as varying from 928 euros per 150 mg vial in Norway to 595 euros in the UK – which means that Norwegians are paying 56% more than the British. Roche would generate huge extra sales if

"Roche has a moral responsibility to set up compassionate programmes until the drug is approved"

health authorities and insurance companies agreed to fund the use of Herceptin in an adjuvant setting, so funders could reasonably insist on a significant drop in price.

But this remains a very expensive drug and health budgets in Europe are static or shrinking. There may be scope for shifting money from less effective drugs. Cardoso suggests that taxanes, which cost around 5,850 euros for a single course of treatment, offer less value for money. "If we can only afford to use taxanes in a small minority of patients, that would be less bad than not having Herceptin, because the effect of Herceptin is much higher."

However, countries such as Hungary already effectively restrict access to taxanes, and some cannot afford to fully fund Herceptin even for women with metastases. In Romania patients with advanced breast cancer sometimes have to wait months for the drug, while in Serbia access is limited by age (under 40 years)

Access to adjuvant Herceptin depends on where you live

✘ **Belgium**	Adjuvant Herceptin will not be available until mid-2006.
✘ **Czech republic**	Herceptin is funded for metastatic disease only. It is possible that funding will be available for adjuvant Herceptin after EMEA approval, at least for high-risk patients.
✔ **France**	Adjuvant Herceptin is funded. Prescription is on a patient-by-patient basis, according to recommendations of a temporary protocol for treatment (see www.e-cancer.fr/medias/pttdefeng2710.pdf), which are based on the HERA trial and include compulsory cardiac monitoring.
✘ **Germany**	The public health insurance does not fund adjuvant Herceptin in general, though a handful of women have won access by going through the courts. Some clinics offer it anyway, because they believe the state insurance will have to pay up, sooner or later.
✘ **Greece**	Herceptin is authorised for use in metastatic breast cancer only.
✔ **Ireland**	There are no problems getting access to adjuvant Herceptin.
✔ **Italy**	As of 31 December 2005, adjuvant Herceptin has been available reimbursed, on a patient-by-patient basis, for women with node-positive HER2+ breast cancer that is also oestrogen and/or progesterone negative. A policy decision on funding adjuvant Herceptin is expected in July.
✔ **The Netherlands**	Herceptin is set to receive reimbursement approval immediately after EMEA approval. Reimbursement will be retrospective from 1 January 2006, providing approval is gained in 2006.
✘ **Poland**	Access to adjuvant Herceptin is restricted to patients at high risk (young, node negative…)
✔ **Portugal**	Each hospital has its own budget, but most will pay for adjuvant Herceptin.
✘ **Romania**	Herceptin is authorised for use in metastatic breast cancer only, and even then, only by appeal to the Health Ministry. Approval can take 2–3 months. Most women are tested for HER2 status at diagnosis.
✘ **Serbia**	Herceptin is restricted to individual high-risk patients, and access will probably continue to be partial even after EMEA approval. Even in the metastatic setting access is restricted by age (up-to 40), performance status (ECOG lower than 2), and previous chemotherapy regimens (less than 2, and should include anthracycline regimens). Testing for HER2+ is not yet routine.
✔ **Slovenia**	Adjuvant Herceptin has been authorised for use (and reimbursement) since July 2005.
✘ **Spain**	Reimbursement is not yet approved; local reimbursement and commercialisation approval is expected to take approximately six months after EMEA approval.
✔ **Sweden**	Most patients can get access to adjuvant Herceptin, however some are still having difficulties because of budget restrictions.
✔ **Switzerland**	There are no problems getting access to adjuvant Herceptin.
✘ **UK**	Funding policies vary from area to area. Fewer than 30% of oncologists say they can always prescribe adjuvant Herceptin; the rest say they can prescribe it sometimes or never. Once EMEA has made its ruling, a decision on funding adjuvant Herceptin will be fast-tracked.

Sources: Europa Donna national representatives, Roche press office, individual clinicians

"Herceptin could be cost-effective if health improvements are large enough and/or discounts are given"

ECOG status and previous chemotherapy regimens (less than two, one of which must have been an anthracycline).

It seems likely that less affluent countries, including the Czech Republic, Poland, Serbia, and probably Hungary and Bulgaria, may restrict adjuvant Herceptin to high-risk HER2+ patients, if they fund it at all. Cardoso argues that this is not as good a compromise as it might seem, because the biology of the tumour is now seen as a far more important predictor of risk than traditional indicators such as nodal status or size.

A SIGN OF THINGS TO COME

If Herceptin was unique, this would be a short-term problem. But Herceptin-style drugs are the story of the future. Unlike cytotoxics, which were identified through mass-screening tens of thousands of compounds, the new class of targeted drugs are designed using high-tech expensive molecular biology techniques.

New drugs are already in the pipeline for HER2 breast cancer, including GlaxoSmithKline's "pan-HER" lapatinib, which is designed to overcome some of the problems of resistance to Herceptin, and is currently in phase III trials. With targeted drugs also in the pipeline for other cancers, will our health systems be able to cope?

Cardoso, who grew up and did her medical training in Portugal, is pessimistic about the ability of less affluent countries and sections of society to access the new drugs. "We are clearly heading towards different medicines in different countries, and increasingly different medicines within countries – a medicine for the rich and a medicine for the poor."

She believes the solution lies in researching the genetic signature of tumours to end the wasteful carpet bombing approach currently in use. If we knew how to identify the 50% of patients with HER2+ breast cancer who respond to Herceptin, we could halve spending on the drug. The same goes for the other drugs used in cancer – anthracyclines, taxanes, aromatase inhibitors, hormonal therapies – none of which are equally effective in all patients. "We need to identify who responds to what, so we spend our money wisely."

Cardoso also mentions the FINHER trial, which revealed results very similar to the other four trials, using only 9 weeks of Herceptin instead of one year.

Putting money into a trial that directly compared 9 weeks to one year of Herceptin could lead to a huge reduction in the overall bill.

The problem is, drugs companies prefer to focus their research on coming up with new drugs to put on the market, rather than finding ways to diminish the market for drugs they are currently trying to sell. That leaves it up to governments to fund such studies, but they too are proving hard to convince, as Cardoso recently learnt when trying to drum up funding for the MINDACT trial, which aims to identify breast cancer patients who do not need chemotherapy.

One option might be to use the regulatory process to oblige companies to carry out further research after their products have come to market, as a condition of approval. However, this approach has been tried in the US, and has proved hard to enforce.

Cardoso argues that governments and the pharmaceutical industry share responsibility for ensuring that research into effectiveness, which could lead to more accurate use of drugs, is carried out. She wants health ministers to get around the table with researchers, health insurance agencies and the regulators to find a way forward, arguing that both governments and pharmaceutical companies will be losers if these drugs prove too expensive to reimburse.

This does make sense, but if it is ever to happen, it will be up to the academic cancer community to help set the agenda. Which means that the next time a very promising designer drug comes along, commentators writing in high-profile journals need to think, among other things, about what is likely to propel health ministers, like the UK Secretary of State, into taking premature policy decisions that undermine the regulatory process, and what might instead help propel them to a forum where all the main players can sit down together and discuss a rational and long-term approach that will ensure that all of Europe's cancer patients get the benefit from the huge potential of the era of designer drugs that has just begun.