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Lesley Fallowfield

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We don't have to be a year behind

Kathy Redmond ■ EDITOR

Late last year, US patients with advanced renal cell cancer gained access to an oral multi-kinase inhibitor, Nexavar (sorafinib) – the first new drug approved for this disease in the last 10 years. Manufacturer Bayer had filed an application for approval with the European Medicines Agency (EMEA) around the same time as its application to the US Food and Drug Administration (FDA). However, the company states that, pending a favourable review, it does not expect the agent to become available to patients in Europe until late 2006 – nearly one year later than in the US.

In January 2006, Pfizer secured FDA approval for its multi-tyrosine kinase inhibitor Sutent (sunitinib) for the treatment of gastro-intestinal stromal tumours (GIST) and advanced renal cell cancer. Pfizer had submitted its marketing approval application for Sutent to EMEA last autumn, but a decision is not expected until later this year.

Patients with advanced renal cell cancer have a poor prognosis and few therapeutic alternatives. The FDA granted fast track status to both products because of their potential to provide important therapeutic benefit over currently available therapies. They made a decision on Nexavar in 162 days and on Sutent in 148 days. Similar patients in Europe, however, still face significant delays in accessing two potentially life-extending drugs that have already been deemed approvable by a leading regulatory agency. Strangely there is no public outcry about this, in total contrast to the scenario currently being played out with Herceptin (trastuzumab).

Europe is lagging a long way behind the US in terms of cancer drug approval times. In some countries, pricing and reimbursement negotiations create additional delays. A new fast-tracking assessment procedure was introduced by EMEA in November 2005 for drugs of major therapeutic benefit that address significant unmet need. The accelerated assessment procedure reduces the time limit for the evaluation of drugs from 210 days to 150 days. At least 80 of these days must be allocated to scientific analysis of the data.

However, the translation and decision-making procedures that follow can add a further two to three months to a drug's approval time, as decisions go back and forth between EMEA, the member states and the Commission.

Recent attempts to speed this process have been little more than a trimming exercise. Commission officials and legislators alike have failed to weed out unnecessary bureaucracy, which continues to impede patient access to innovative cancer drugs in Europe. The European cancer community has a responsibility to help policy makers redress this unjust situation.

Lesley Fallowfield: getting the message across

Marc Beishon

It was while studying the benefits of offering patients a choice between radical and breast-conserving therapy that Lesley Fallowfield first demonstrated the importance of doctor-patient communication. Her findings haven't always been welcome, but cancer doctors who are now getting trained in talking to patients, and to each other, should know whom to thank.

Quality is a word that occurs regularly in discussions with Lesley Fallowfield, one of the pioneers of psycho-oncology, the branch of oncology concerned with behavioural, social and psychological aspects of cancer care and treatment.

Fallowfield, professor of psychosocial oncology at the new Brighton and Sussex medical school, in England, and director of Cancer Research UK's psycho-oncology group, has led passionate and forceful initiatives to establish quality-of-life measures as currency among the survival rate number crunchers. Further, she has made it her business to examine and expose one of the most sensitive areas of clinical work – the quality of doctor–patient communications in cancer consultations. And her work is now influencing the quality and success of almost all cancer areas, from phase I clinical trials to multidisciplinary teamworking to palliative care.

Today, no major cancer centre would dream of running without some of the supportive services that psycho-oncology has helped to develop over the last 20 years or so. It is now a recognised cancer speciality, with international and national associations, and a rapidly expanding portfolio of research work.

But as Fallowfield comments, it was a struggle in the early years to get psycho-oncology on the agenda. "If you were really lucky you'd get a poster presentation on the last afternoon of a conference in the most obscure room, and manage to show it to half a dozen people," she says. "We are now giving keynotes at the plenary sessions of most major cancer conferences."

The entrenched attitudes of the medical profession to what can still be seen as 'soft' skills, and pigeon holing psycho-oncology into a purely supportive role for alleviating patient depression and anxiety, have been among the major barriers faced by Fallowfield. She recognises that doctors can be defensive and resistant to change with good reason. "It can mean them acknowledging that what they've been doing, or omitting to do, may have been damaging patients for years," she says.

When Fallowfield first started her psycho-

ANTHONY HARVEY / PA

Team work. Lesley Fallowfield with data-monitors Clare Coxon and Louise Parlour, who process hundreds of questionnaires from clinical trials each week

oncology career, early exchanges with the medical profession were often confrontational. "I started out predominantly as a patient advocate," she says. "Now, the more time I've spent with healthcare professionals and watched and recorded them struggling in difficult clinical situations, the more I've realised that we just haven't been giving them the support they need. You'll never get doctors and nurses closer to the needs of patients and their families if no one cares about how they are coping with things."

Nevertheless, a degree of friction was perhaps necessary for Fallowfield to make her mark. She recalls one talk to the UK's Royal College of Physicians where she was berating doctors for concentrating on quantity rather than quality of life. "I was rather strident and attacking and was given a very rough ride," she says. "Afterwards, Dame Cicely Saunders, founder of the world's first modern hospice, and an important person for me, came up and said, 'Don't give up – the only reason they are so angry is because basically you are right.'"

Trusting her instinct that she's onto something when tempers rise has played its part in her research choices to date, but much networking among senior oncologists throughout the UK has resulted in considerable buy-in to Fallowfield's ideas. Her team is now a partner in major national and international research initiatives, particularly quality-of-life measurement in clinical trials such as the UK's huge ovarian cancer screening study, which is evaluating the psychosocial impact and acceptability of different screening methods in 187,000 women. Her team's communication skills training for cancer teams, meanwhile, is being rolled out as part of England's Cancer Plan.

Fallowfield says it has been the willingness, despite reservations, of senior oncologists to

"I've never regretted doing nursing – it's given me insight into the research world I now inhabit"

allow pyscho-oncology research teams into their centres that has paved the way for such work, and she's extremely grateful to them. Her own background in healthcare has also helped – as did the unstinting support and backing of an often controversial mentor, surgeon Michael Baum, who gave her the first break in the field.

"I started out as a nurse at Guy's Hospital, London, after a traditional girl's grammar school education that favoured the arts." She feels that although medicine would have suited her well, "I've never regretted doing nursing – it's given me a great insight into the research world I now inhabit." While bringing up a young family, Fallowfield took several courses for fun at the UK's Open University (where students work from home) "as I didn't want my brain to seize up – and I discovered psychology". She took a BSc in experimental psychology ("which we feel is the superior arm of psychology") at the University of Sussex and progressed to a doctorate.

Things were going very well, with Fallowfield set for a successful career in psychophysics, until a best friend was diagnosed with acute myeloid leukaemia, and died. "She said I should do some research on why doctors don't tell patients enough about their disease, and her death had a profound effect on me," says Fallowfield, who was determined from then on to pursue a career in cancer. "I do think it can be dangerous to try and work through your own feelings by helping others, but it can give you a determination to change things and keeps you going through the tough times, and believe me it was very tough at the beginning in psycho-oncology."

Fallowfield was fortunate to find several mentors who enabled her to switch her psychological expertise to oncology, none more helpful than breast cancer surgeon Michael Baum, then at King's College Hospital in London, who gave her a first cancer job. She had been working on ways of measuring perceptual problems and sensory losses reported by patients with optic nerve damage, which clinical tests at the time were unable to detect reliably, and put it to Baum that her skills lay in "measuring things people thought were immeasurable".

Baum – himself interested in quality of life and an outspoken pioneer in patient communication about cancer – guided Fallowfield in her early work. She also benefited from working with Peter Selby and Robert Souhami, other top cancer physicians in the UK community who have both been clinical consultants to her psycho-oncology group and whom she describes as "inspirational individuals without whom I'd have never ever have achieved so much."

It was with Baum that she carried out her first study – and stepped immediately into controversy. "We looked at a trial where women were randomised to have either a mastectomy or breast conservation. Before we started, it was assumed that all the psychological morbidity associated with breast cancer treatment was due to breast removal, so when trials around the world indicated success for conservation surgery in women with early-stage disease it was thought that we could save them from both mutilation and distress. But our study showed no difference between mastectomy and conservation for psychological morbidity and also sexual dysfunction."

This finding came under fire, she recalls painfully, from many, including breast cancer support groups. "I'll always remember being at a conference in the US when a vociferous member of a group called out, 'Dr Fallowfield, I hope you're proud of giving surgeons an excuse to hack off women's breasts.' It's difficult to fly in the face of medical orthodoxy when there are such passionate feelings." A constant theme since then has been to evaluate and follow-up research to ensure the quality of findings and

With children Jonathan, who is training to be a gastroenterologist, and Caroline, a paediatric nurse

make the most convincing case – which has often been an exhausting process.

Fallowfield's explanation for the counterintuitive results was that, while body image was important, it tended to assume significance only after women had coped with the immediate distress of having a potentially life-threatening disease. Further, in a study of women treated by surgeons who offered choice between different types of surgery or not, she found that those women offered a choice fared better psychologically – but it wasn't the treatment or the choice that made the difference, rather the communication from the doctor. "We found that the 'choice' surgeons offered so much more information about why they would recommend one treatment. We followed women in the study for three years and found that the first consultation was so vital in determining outcomes for adjustment, anxiety and depression – which led us to start looking at communication issues in more detail."

It was obvious, she adds, that the better communicators had patients who were better adapted to their disease. However, too many doctors did not – and still don't – receive decent training in this area. Apart from being a great talker and listener herself, Fallowfield became so interested in communication skills that she went into training with a group called the US Task Force on the Medical Interview, which evolved into the American Academy on Physician and Patient, in 1993. "This was run by a truly great man, Professor Mack Lipkin [of New York University], who had developed a model of communication skills training for senior doctors. I trained for six years with him, going over to the States in my spare time."

Despite such initiatives, it is only relatively recently that medical schools and national bodies have realised that communications is a core competency for a doctor, and some have indeed started to implement more training in their curricula. But as Fallowfield points out, any change at junior level could take many years to be seen in widespread practice, which is why

"We found that the first consultation was vital in determining adjustment, anxiety and depression"

ANTHONY HARVEY / PA

– impatient for action – she homed in on senior doctor training as making the fastest impact. In any case, junior doctors, she says, are more likely to be influenced by their senior role models. "We needed top-down as well as bottom-up training initiatives – and quickly."

By this stage, Fallowfield had been working on quality-of-life assessment in clinical trials with centres around the UK, and was able to call in some favours from senior oncologists for her communications work. "Although people said I was mad to try this, some very high profile oncologists attended the initial courses and then became vociferous supporters, encouraging others to come along." A communication skills training programme has now been developed over the past 15 years or so, a process that she says has been rather like developing a drug through the various phases: "Is it acceptable, what are the toxicities involved, how long should 'treatment' last, where should it be delivered and by whom?"

What Fallowfield and colleagues discovered was a dose–response relationship; namely, that only an intensive three-day residential programme can make a difference to long-term communication outcomes in the clinic. This has been established with a pretty large – and rare – randomised trial written up in the *Lancet* (2002, 359: 650-656), involving 34 cancer centres and 5,000 patients, with patient–doctor interviews followed up at three and 12 months. "No one had clearly demonstrated that you can transfer such skills to the clinic before," she says, "and moreover that the effects were lasting."

The communication model, which has since attracted international interest, uses actors to play roles, and equips doctors with a way to self-critique their own interviews. "It's quite extraordinary how seldom people process what works and doesn't work well for them," says Fallowfield. Doctors are generally unaware, for example, of the way they ask questions. They often use closed, leading and multiple questions that elicit inaccurate data, and frequently they don't respond empathetically – or completely bypass – patients' more psychosocial concerns. Jargon and euphemisms are also rife. "Patients know you can't fix everything and don't expect it. But they'll never forgive you for not acknowledging that they are having a tough time," she says.

In case anyone is in any doubt about the role of communication, Fallowfield rattles off a list of benefits. They include having a more professionally and personally rewarding job, making better diagnoses and fewer errors, and managing symptoms better (both physical and mental). "Patients who understand the rationale for lifestyle changes are also more likely to carry out requests," says Fallowfield. "Hospital stays and complications are lower as well. It's not about being kind – it's about being a better scientist." And one for the bottom line – litigation costs could well be lower.

Perhaps the clincher is protecting against 'burn-out', which Fallowfield feels is far too high among oncologists. "Poor communications can contribute to burn-out, or vice versa – it works both ways – but when you look at what a typical hospital doctor does across a 40-year career you'll find they conduct 150,000 to 200,000 interviews with patients and families – spending more time on this than drawing blood or wielding a scalpel. When you consider that in training doctors spend more time learning techniques they'll barely ever use than on communication, you can see why we've got a problem, and why communication must be a core competency."

Few teams actually function as an integrated unit, and there can be alarming cracks in the façade

A spin-off from this work is communication within the much vaunted multidisciplinary cancer team. As Fallowfield and her researchers have discovered, because multidisciplinary working demands resources above those usually on offer, few teams actually function as an integrated unit and there can be alarming cracks in the façade. True to form, evidence has been gathered painstakingly by following patients as they see various team members and recording their impressions.

"We find out how the team members see each other and what they feel their roles are, and take them away and show them what happened in practice – for some it can be quite shocking." A simple example is a colorectal team where a nurse specialist had missed a team meeting and talked to a patient about an impending colostomy – when a decision had been made to carry out a sphincter-saving operation. Sometimes raising the bar can be as simple as hiring a coordinator, or providing a room big enough for people to meet in, a car parking space, a crèche or a lunch, or start times that fit team members with young families.

But the issues involved in multidisciplinary working can go much deeper, ranging from the inhibiting impact of powerful egos among the senior doctors, to lack of awareness of team members' information-giving roles. Fallowfield's group have reported the unwillingness of anyone in the team to discuss with patients psychosocial issues such as sexual dysfunction, and frequently a lack of any discussion about family history. Doctors can wrongly assume someone else is covering these issues, or delegate the role to nurses who might not have taken part in the multidisciplinary discussions. Fallowfield adds that she's finding now that many oncology staff are requesting specific training in communication with their colleagues, and some consider it more pressing than dealing with patients.

As an ex-nurse herself, she also makes the observation that, contrary to what is widely believed at least in Britain, "people [in clinical teams] respected each other a lot more in my day", despite a more rigid hierarchy, especially between doctors and nurses, in those days. "As nurses have struggled to gain recognition as a more academic profession they have lost a lot of respect that people genuinely had for nurses with superlative practical skills. Today, many doctors don't even know the names of the nurses on the wards, and nurses don't seem to accompany doctors on ward rounds, so it's little wonder that few know what has been said to a patient."

After working her way up through the ranks as a psycho-oncology academic, Fallowfield became a professor at University College London in 1997, and in 2001 moved her group to the present location on the campus of the University of Sussex, joining the new medical school a little later. Her work has continued apace and cross-fertilised in various ways, for example in the clinical trials area, where communication, quality of life and new psychometric tests are all pertinent topics.

The communication aspect is critical when recruiting people to clinical trials, says Fallowfield. "Doctors often have idiosyncratic ways of discussing trials with patients; others think it will take too much time – a particular problem now that doctors have to meet targets for rapid throughput of patients. They also tend to approach only certain types of patients. We spent weeks filming doctors and research nurses talking about trials, and have produced educational materials that help them with time management, dealing with difficult personalities and how to explain concepts such as randomisation."

Given the gross shortage of patients enrolled in trials, this is clearly important work. While recognising that some trials are genuinely pretty

hard to explain, Fallowfield says there are some key principles to learn, one of the most important being to establish a 'platform of certainty' and not say you are unsure how to proceed. "This means saying, for example, 'I know the best treatment is this and we'll offer it to you, but we're always interested in improving things and you may have heard about this…' No one wants to hear that they've got cancer and their doctor doesn't know how to treat them."

She was surprised to find that there was hardly any material available to equip oncologists with an explanation of the core concept of randomisation. "We had to do some original work on this before developing the training materials," she says.

Measuring success of this training is hard, as there are many factors that can affect the uptake of trials, but her group is working with oncologists in Wales, a fairly self-contained and small country, randomising multidisciplinary teams to receive the training or not. "We think the key outcome is not how many patients go into trials, but how many eligible patients are at least offered them," she adds.

The importance of psycho-oncology also comes into its own when measuring the effects of clinical trials and everyday treatment. When Fallowfield first looked at quality-of-life measures, she found hopelessly outdated or inappropriate indicators used by clinicians. "They would measure things like whether someone went back to work or not," she says. She's since helped to develop and introduce new psychometric tools based on patient feedback, particularly for breast cancer, but she notes that new and updated methods will always be necessary because of rapidly changing treatment regimens.

Fallowfield has particular concerns about the later side effects of treatments, "It must be awful to successfully treat childhood cancer only to find that other cancers, cognitive impairments and fertility problems develop later on." She adds: "A lot of adult treatment trials are closing earlier than originally designed, and we don't always have enough long-term follow-up data on side effects, which is worrying."

Fallowfield has continued to highlight other factors affecting quality of life, since that first breast mastectomy versus conservation study. She believes that while it is reasonable for oncologists to home in on potentially life-threatening side effects, such as endometrial cancers or cardiovascular problems, other non-life threatening ones may receive too little attention. One study that made the news recently showed that hot flushes associated with hormone treatment can deter women from continuing with the regimen. When asked why some doctors don't take hot flushes seriously enough and why insufficient effort went into relieving them, she was quoted by the BBC as saying: "No one ever died from one except from embarrassment. A Nobel prize should go to the person who stops women having hot flushes while undergoing such treatment. If quality of life was measured more often in clinics, not just clinical trials, then people would realise the extent of these non-life-threatening problems that patients suffer."

A study where quality-of-life measures were 'off the scale' (in a positive direction) was the UK ALMANAC trial of women having a sentinel node biopsy versus conventional axillary resection. Using a quality-of-life questionnaire, Fallowfield's team has shown that good arm movement, which is preserved using the sentinel node biopsy, is a highly valued outcome influencing overall quality of life.

The challenge now, she says, is to move quality-of-life measures into routine clinical assessments. "We have won the case for their use in clinical trials, but not in the clinic. Part of the answer lies in developing computerised tools that doctors can use quickly in the clinic. I

"Doctors often have idiosyncratic ways of discussing trials with patients"

"A Nobel prize should go to the person who stops women having hot flushes while receiving treatment"

suspect it would be a bold clinician who would change cancer management based on a patient's quality-of-life scores, yet the same doctor would have no problem changing tack if a tumour marker had gone off the scale. We hear so much about translational research – I wish people would show the same enthusiasm for translating some of our positive psychosocial research."

Nevertheless, the achievements so far should not be underestimated, she says. "The drive to improve communication skills training since our incontrovertible demonstration of efficacy has really taken hold. The wide availability of patient referral and advocacy services in most countries, while they should never be an alternative to good patient–clinician communication, has also been a great advance. Specialist cancer nurses, especially in breast clinics, is another great plus, while the UK's hospice movement and research into end-of-life issues is a world leader."

The immediate work programme for Fallowfield's unit also includes moving forward with the multidisciplinary teamworking research, and looking at underserved cancer patients such as those with brain, head and neck and prostate tumours. "We are also collaborating with cancer centres that talk to patients about participating in phase I trials as most of the work to date has focused on phase III work," she says.

Properly testing complementary therapies is also on the agenda. "I'm wholeheartedly in favour of some of the therapies that assist patients in other ways, such as aromatherapy, but these must always be evaluated systematically. When people are diagnosed with cancer they can develop a kind of 'skin hunger' – often no one touches them anymore, apart from when carrying out clinical procedures. Relaxed people also don't feel as much pain."

Personally, she would like a bit more relaxation, having worked flat out on her research for some 22 years (including many international speaking and training engagements where she is in great demand). It would be remiss here not to mention her deputy (and golf partner) Valerie Jenkins, who co-ordinates and supervises much of the research of the 20 strong unit, where a psychology degree seems to be de rigueur for the research fellows. Jenkins, like Fallowfield, was originally a nurse before becoming a psychologist, so they share similar insights in the field of psycho-oncology.

Family life is very important to Fallowfield. She has two children, both in healthcare – a son training to be a gastroenterologist, and a daughter who is a paediatric nurse. She also has a 'wonderful' baby grandson.

"Life has been too chaotic over the past few years to enjoy fully my many interests. I adore music and have eclectic tastes – I'm as happy at a Rolling Stones concert as at the opera; I also read copious numbers of books, anything from biographies to Michael Crichton novels.

"I'm an enthusiastic but extraordinarily bad golfer, so I'd really like to get my handicap down this year. Developing a better golf swing is rather like becoming a better communicator – you have to stop doing something old if you want to do something new, and I've got into some very bad old habits." Hopefully her recent knee surgery will permit her to do more walking on the Sussex Downs and along the seafront in her beloved Brighton.

"I think I'll see out my retirement here – if I'd ever been motivated by money I would have jumped ship a long time ago."

There's an old joke that Fallowfield likes to tell about a drunk who's lost his keys. "Someone sees him looking under a street lamp – 'Why are you looking there?' they ask. 'The light's better,' he replies." It's comforting to know there is someone exploring the darker areas of cancer – and producing quality evidence, of course.

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

www.thisisthesentinel.co.uk Thursday, September 29, 2005 30p MIDLANDS NEWSPAPER OF THE YEAR

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?

ABSOLUTELY FREE FREE Underlay Grippers Fitting & Delivery ON ALL ORDERS HOME CHOOSE SERVICE AVAILABLE BEAT IT! B&A CARPETS 01782 205414

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

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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.

Phase III trials in oncology

Setting standards of care?

Siegfried Seeber and Ada H Braun*

Survival data from phase III trials can be very misleading because patients are not offered the best follow-up therapy argue **Siegfried Seeber** and **Ada Braun** in *CancerWorld's* new Forum section. **Emma Mason** canvassed clinical trial leaders, and presents their responses in the Debate section that follows.

For many years, oncologists worldwide have advised their patients to enrol in clinical trials for optimum assessment of treatments, monitoring and follow-up, and consequently better survival and quality of life compared with routine management. Randomised phase III studies that have survival as the primary endpoint have been the indisputable basis for setting new standards and launching new drugs, combinations and multimodal treatment options into clinical oncology practice. Such studies may be misleading, however, when enrolled patients have not received optimum follow-up therapy after failure of the assigned treatment.

In recent licensing trials for agents targeted at breast cancer, restricted access to post-study chemotherapy has yielded 'superior' survival data for investigational drug combinations versus single-agent therapy, with remarkably poor survival in all cohorts.[1] A number of these trials have resulted in approval of specific regimens. In a study showing 'superior survival' for capecitabine plus docetaxel compared with docetaxel alone (14.5 vs 11.5 months, respectively) in 511 anthracycline-pretreated patients, only 17% of patients in the docetaxel-alone arm received post-study capecitabine, and overall only 30% received post-study vinorelbine and 20% 5-fluorouracil.[1] Especially given the very short median times to treatment failure reported (4.0 and 2.8 months), it is against routine practice to offer only two-thirds third-line chemotherapy. Capecitabine was consequently registered for breast cancer therapy, with docetaxel as the mandatory combination partner.

Gemcitabine was approved for combination therapy only, because a licensing trial comparing gemcitabine plus paclitaxel with paclitaxel alone stated that "gemcitabine plus taxol provides significant overall survival advantage over taxol."[2] The advantage of combination over sequential single-agent therapy is undetermined, however. Again, unsatisfactory post-study access to active agents probably accounted for the unacceptable median survival data reported (18.5 vs 15 months, respectively).

In a recent randomised trial of trastuzumab plus docetaxel in 188 patients with HER2-positive metastatic

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TOM STEWART / CORBIS

breast cancer, only 48% of the taxotere-alone control group were documented to receive the antibody at progress! Yet it was concluded that the addition of trastuzumab to docetaxel "improves all clinical outcome parameters, including survival."[3] Would this hold true if patients from the control group had received vinorelbine plus trastuzumab after taxotere failure? Albeit active, the latter combination is still 'illegal'.

Should such studies set new standards of care for our patients? For 197 unselected consecutive patients treated in our centre in the pre-trastuzumab era (between 1 January 1995 and 31 December 1999), the median survival of breast cancer patients first-line for treatment of metastatic disease was 36 months, with a 35% four-year survival (C Pohlkamp, A Welt and S Seeber, unpublished data). Of 146 patients with inoperable liver metastases, 25% survived for over 48 months, and 14% for over 60 months – some for over eight years. In many cases, clinical responses were observed even in the sixth or seventh line (see Case Report, opposite). These patients require close monitoring, early intervention at progression, and individualised multimodal therapy employing effective drugs either singly or in adequate combinations, irrespective of their registration status. Dose-dense regimens should be used in critical phases and 'softer' interims involving oral maintenance therapy as well as locoregional treatment options (e.g. surgery, interventional radiology or hepatic artery infusions). Experienced physicians are not impressed by studies claiming a survival advantage of 15.4 vs 12.7 months for docetaxel versus paclitaxel in metastasised breast cancer,[4] a result advertised as a 'highlight' of the 2003 ECCO.

In stage 4 non-small-cell lung cancer, it took 408 patients to prove that combining paclitaxel with carboplatin is as effective as vinorelbine plus cisplatin,[5] with equally poor median survival (8 months), and one-year survival rates (38% vs 36%). In this and a similar ECOG (Eastern Cooperative Oncology Group) trial of four two-drug combinations, there was no routine crossover at treatment failure; nor did the majority of patients receive adequate second-line or third-line treatment. However, second-line taxotere can prolong life in platinum-refractory patients, and even third-line irinotecan can induce significant responses lasting up to one year.[6]

Unsatisfactory post-study access to active agents may account for the unacceptable median survival

Representative case report: breast cancer

57-year-old female patient with metastatic breast cancer; history of 15 lines of chemotherapy; now good performance status
Note that the patient has been treated off-label since the 2nd line of chemotherapy; alopecia was induced only under EC- (epirubicin/cyclophosphamide) and taxane-based treatment; response to treatment was assessed at least every 3 weeks using ultrasonography and serum markers (including CA 15-3 and LDH) or at least every 9–12 weeks using CT, MRI and/or X-rays; pulmonary metastases remained in good partial remission throughout treatment; any attempt to ascribe the relative contribution of individual drugs to the overall survival of the patient appears absurd.

09/1993	First diagnosis of breast cancer (invasive ductal adenocarcinoma; left breast) T1 N1 (2/11) M0; G2; oestrogen/progesterone receptor (ER/PR) negative; HER2+++ (immunohistochemistry) breast-conserving surgery, adjuvant radiotherapy left breast, 6 cycles of adjuvant chemotherapy (CMF; cyclophosphamide, methotrexate, 5-fluorouracil) in a peripheral hospital
09/1994	Increase in CA 15-3 tumour marker, indicative of relapse
07/1995	Total mastectomy on local recurrence; tumour now ER+, PR-; adjuvant tamoxifen therapy
01/1996	Once again increase in CA 15-3 tumour marker; first diagnosis of pulmonary metastases; treatment with the aromatase inhibitor formestane
12/1997	Progression of pulmonary metastases; first diagnosis of liver and bone metastases
01/1998	Treatment with the progestin medroxyprogesterone acetate (MPA) to no avail
04/1998	Chemotherapy with epirubicin and cyclophosphamide (EC; 1st line chemotherapy for metastatic disease); clinical response for more than 6 months
03/1999	Upon patient request of hair-sparing therapy, treatment with vinorelbine and 5-fluorouracil within a clinical trial (2nd line; until 09/1999); good clinical response
03/2000	Radiotherapy of right ileosacrum for pain control (30 Gy)
04/2000	Increase in CA15-3; docetaxel (3rd line) results in partial remission of hepatic lesions
10/2000	Bridging therapy with the aromatase inactivator exemestane proved to be ineffective
12/2000	Raf kinase inhibitor (BAY 43-9006; 4th line; phase I clinical trial); minor response for 5 months with excellent quality of life
06/2001	Fulminant hepatic disease progression (CA 15-3 increase up to 18,750); 3x monthly locoregional therapy (hepatic artery infusions) with mitomycin C plus 5-fluorouracil (5th line); major response and recovered performance status
09/2001	Oral maintenance therapy using capecitabine (6th line)
06/2002	Progressive disease (liver); oral chemotherapy with CMP (cyclophosphamide, methotrexate, prednisone; 7th line) induces partial response for 2 months
08/2002	Increase in CA 15-3; mitoxantrone therapy (8th line); clinical response for 3 months
11/2002	Increase in CA 15-3; combination therapy with vinorelbine and epirubicin (9th line)
12/2002	Although minor remission of hepatic lesions, due to toxicity therapy is continued with gemcitabine (10th line); time to disease progression is 3 months
03/2003	Trastuzumab (11th line) induces regression of hepatic and pulmonary lesions
09/2003	Tumour marker turnaround; treatment with vinorelbine (12th line)
01/2004	Oral capecitabine maintenance therapy (13th line)
06/2004	Upon marker progression, treatment with oral CMP (cyclophosphamide, methotrexate, prednisone; 14th line)
09/2004	Progressive disease (liver, pelvis, ascites); treatment with paclitaxel single-agent (15th line)
10/2004	Despite clinical response, change of therapy due to toxicity (polyneuropathy); docetaxel (16th line) induces minor response
12/2004	Since 12/2004, treatment paused; ultrasonography shows continued response but evidence of developing liver cirrhosis; good performance status (WHO 1)

In ovarian cancer, evidence-based medicine usually favours taxol plus carboplatin as induction treatment, with topotecan or liposomal doxorubicin for platinum-resistant tumours. Phase III studies are underway with overall survival as the primary endpoint.[7] Our mono-institutional analysis involves 77 unselected consecutive patients with FIGO stage 3 or 4 ovarian carcinoma, who, between 1 January 1993 and 31 December 2003, received an average of six treatment regimens, and early surgical interventions whenever applicable (C Brinkmann, J Hense and S Seeber, unpublished data). Therapies were adjusted on an individualised basis following any signs of disease progression, producing a median overall survival of 55 months in the total population and 63 months in stage 3 patients. Early adaptation of treatment regimens is mandatory for good patient outcome, and therapeutic interventions can prolong good-quality survival even late in the disease course.

Increasing evidence suggests that chemotherapy in hormone-refractory prostate cancer improves both quality of life and survival. Tannock et al.[8] examined docetaxel plus prednisone and mitoxantrone plus prednisone in such patients. Disconcertingly, they reported "superior survival" for the docetaxel arm, while crossover therapy after mitoxantrone failure was documented in only 20% of patients, with no other follow-up treatments specified. In our experience, second-line or third-line drugs can induce valuable responses over several months (A Schneider and S Seeber, unpublished data). Hence, the issue is not whether a mitoxantrone- or a taxane-based combination alone improves patient outcome, but which combinations or sequences are most rational.

Even colorectal cancer patients have suffered inferior survival in phase III studies because of constrained second-line treatment options. Goldberg et al.[9] reported that IFL (irinotecan, 5-fluorouracil and leucovorin) first-line therapy (also known as the Saltz regimen) was inferior to the FOLFOX regimen (oxaliplatin, 5-fluorouracil and leucovorin), but most patients enrolled in the study did not receive second-line oxaliplatin. Tournigand et al.,[10] comparing FOLFOX6 followed by FOLFIRI (irinotecan, infusional 5-fluorouracil and leucovorin) with the reverse sequence using a crossover design, found no significant difference in survival.

In conclusion, survival of patients with common metastatic cancers is determined not only by the choice of first-line chemotherapy regimen but also by sequentially applied alternative treatments at progression or relapse. Phase III trials documenting superior survival for any given primary chemotherapy in these diseases often offer patients insufficient access to salvage treatment and are therefore misleading. Unfortunately, results emanating from such studies continue to give rise to restricted licensing of mandatory drug combinations, even though physicians need both monotherapeutic and combined usage of active agents, according to a patient's history and preference – especially in advanced metastatic disease.

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Early adaptation of treatment regimens is mandatory for good patient outcome

THE DEBATE

The central charge of the Seeber and Braun article, that patients in phase III trials are offered insufficient access to the best follow-up treatment after the first one has failed, which consequently skews the overall survival data, is contested by other oncologists.

They say that it would be unethical for patients to be denied proper post-trial treatment, and that no physician would ever enter their patients into a trial if they thought that this would happen.

As their first example, Seeber and Braun refer to a 2002 trial of capecitabine (Xeloda) plus docetaxel (Taxotere) combination therapy in patients with advanced breast cancer. "Only 17% of patients in the docetaxel-alone arm received post-study capecitabine, and overall only 30% received post-study vinorelbine and 20% 5-fluorouracil.

"Especially given the very short median times to treatment failure reported (4.0 and 2.8 months), it is against routine practice to offer only two-thirds of patients third-line chemotherapy," write Seeber and Braun.

Seeber told *CancerWorld*: "We … think that a number of recent registration studies do have an ethical problem, and it is by no means understandable that, for instance, in the Xeloda plus Taxotere versus Taxotere alone trial, only a small part of these patients received a crossover or adequate other therapies, although time to progression was very short."

However, Patrick Therasse, director of the data centre at the European Organisation for Research and Treatment of Cancer (EORTC), said: "The situation Seeber is referring to is a fact of life for cancer patients, some of whom will indeed not tolerate a second- or a third-line treatment because of the rapid evolution of their disease or because of their performance status being too low. But this is seen both in clinical trials and outside trials.

"I disagree with his statement, and I don't see why a patient in a clinical trial would have less access to salvage treatment than a patient out of a trial. On the contrary, some patients may even benefit from a crossover and access an investigational treatment that would otherwise not be available to them.

"It would be totally unethical not to be able to offer a patient the best salvage treatment because he has been in a trial; so participation in trials does not decrease access to state-of-the-art salvage treatment. If any physician believed this to be so, there would be no patients entered in clinical trials."

Monica Castiglione, chief executive of the International Breast Cancer Study Group (IBCSG), based in Bern, Switzerland, agreed with Therasse. "I would be very surprised to know that patients did not receive proper treatment after treatment failure in the trials. I cannot imagine ethical committees allowing the conduct of a trial that is mandating for improper treatment after failure. The fact that 'only' two thirds of the patients received a third-line chemotherapy looks to me quite normal. We generally have a number of patients with very aggressive disease to whom we are not able to apply third-line treatment."

Seeber told *CancerWorld*: "During the trials the investigational drugs or combinations were superior regarding time to progression, but according to our experience these trials should not have reported survival gains. Survival in breast cancer, for example, is influenced by the long-term management, including often five and more lines of systemic treatment. In the papers we mentioned there was no satisfactory information on third-line therapies; most probably they had not been done. Indeed only 48% of the patients did receive trastuzumab when their tumours progressed."

But Castiglione said: "There are no data to my knowledge showing a survival benefit for third-line treatments in metastatic breast cancer; so this argument may be quite weak."

She believes that Seeber and Braun's use of the example of prolonging the lives of advanced breast cancer patients with inoperable liver metastases by treating them with several lines of different therapies is, in itself, misleading.

Siegfried Seeber: A drug has to be helpful, but it is nearly impossible to relate overall survival to one drug or one combination

Aron Goldhirsch: Phase IIIs tell us which treatment is better overall. The care of individuals must be extrapolated from the results

Stan Kaye: Using overall survival as an endpoint may fail to take proper account of treatments for relapse

"At the IBCSG we have examined the survival of patients from the time of metastases, and we observed that obviously visceral metastases have a poor survival, but we all know some patients with liver metastases who have survived several years; CNS [central nervous system] metastases have the worst survival, but I have a patient who is now surviving the tenth year. But one case cannot change our policies. We all know some patients who responded to the sixth or seventh chemotherapy. This is also, by far, not the rule, and a number of patients die before you can apply the third or fourth chemotherapy."

In other words, good (or bad) cases, are not good foundations on which to build general rules.

Therasse said: "To demonstrate the efficacy of a new treatment, there is, as yet, no good alternative to robust, randomised phase III trials. Stating better outcome, based on a small institutional survey is dangerous. The role of each clinician and investigator is to ask for more research when this is appropriate (and this is not always justified)."

Aron Goldhirsch, a member of the ethics committee of the European Institute of Oncology, Milan, Italy, said that the Seeber and Braun paper showed "significant confusion between 'on average this treatment is good for you' and knowledge about benefit of treatment for individuals."

He continued: "Phase III trials in oncology typically ignore individual patient care. They are focused on generating evidence on which treatment is better overall. The care of individual patients must be extrapolated from the trials' results; an exercise which is fruitful if selected predictive features are identified (i.e. tailored trials)."

Seeber and Braun suggest that if phase III trials were designed so that overall survival was not their primary endpoint and patients were able to access the best salvage treatment, this would help to prevent trials being "misleading", would prevent restrictive licensing of drugs and drug combinations, and would give patients access to the best salvage treatment after the end of the trial. "Unfortunately, results emanating from such studies [with overall survival as their endpoints] continue to give rise to restricted licensing of mandatory drug combinations, even though physicians need both monotherapeutic and combined usage of active agents, according to a patient's history and preference – especially in advanced metastatic disease," they write.

They say that, as things are at present, doctors are limited by restrictive licensing when considering further treatments if the cancer progresses, and this results in patients receiving less than optimum care.

"Our main point is: allow registration according to study endpoints of improved relapse-free survival or improved time to progression in the different clinical situation," said Seeber. "A drug has to be helpful, but it is nearly impossible to relate overall survival to the action of one drug or

Monica Castiglione: The fact that 'only' two thirds of the patients received a third-line chemotherapy looks quite normal

Patrick Therasse: If physicians thought participation in a trial decreased access to best salvage treatment, no patients would be entered

one combination."

Stan Kaye, professor of medical oncology at the Institute of Cancer Research, the Royal Marsden Hospital, UK, commented: "In principle, it is reasonable to say that phase III trials which use overall survival as an endpoint may fail to take proper account of treatments for relapse, which may be improving in several tumour types. This argues in favour of using progression-free survival as a better endpoint in phase III trials of initial therapy, and regulatory authorities now accept this." *

Castiglione also believes that drugs for metastatic disease should be registered on the basis of results from trials using endpoints of improved relapse-free survival or improved time to progression. But she agrees with Kaye that this is no longer an issue. "Regulatory authorities now accept progression-free survival and other endpoints for trials of metastatic diseases, and they accept disease-free survival for adjuvant trials. So I do not believe that this is a problem."

Goldhirsch is more cautious. "Who is the 'winner' mentality governs the marketing of several treatments, with single drugs or with combinations. Even if regulatory agencies will recognise a more sensitive endpoint, the essence of how marketing determines treatment choice will hardly change."

As to whether restricted licensing adversely affects our understanding about which are the most effective combinations or sequences of second, third or more lines of therapies, Therasse said: "There are many trials addressing these questions of treatment sequence and indications – probably too many as compared to other important questions which will remain unanswered, because there is no drug or no company behind them."

In conclusion, the scientists quoted above all disagree with Seeber and Braun that current phase III trial practice offers patients insufficient access to the best follow-up therapies. There is a general consensus that overall survival is not necessarily the best primary endpoint for a trial and that progression-free survival or improved time to relapse are more sensitive endpoints. However, Therasse and Castiglione believe that this is no longer a problem and that regulatory authorities accept these different endpoints.

The scientists questioned for this article did not think that current practice restricts our understanding of drug combinations or sequences for follow-up therapy, though the manner in which drugs are subsequently marketed was seen as unhelpful. Everyone believed that, at present, drug licensing has to be based on the evidence from large, randomised phase III trials.

The Debate was compiled by **Emma Mason**

WHAT DO YOU THINK?

CancerWorld would like to know what your thoughts or experiences are on these issues. Is there a problem with the way phase III trials are run and their effect on the way drugs are licensed? Do patients suffer from lack of proper follow-up treatment at the end of their trials? Contact us at editor@esoncology.org and let us know.

*The European Medicines Agency's Guideline On The Evaluation Of Anticancer Medicinal Products In Man, which gives details about their policy on crossover and use of overall survival versus disease-free or progression-free survival as a primary endpoint, can be found at www.emea.eu.int/pdfs/human/ewp/020595en.pdf

Mr Hodgkin's disease

Peter McIntyre

Volker Diehl cultured the cells that characterise Hodgkin's disease when everyone else had failed. He has high hopes that molecular medicine will throw light on many questions that remain unanswered. But he stresses that it is the disciplined clinical work on the wards that saves lives in this disease, where the line between cure and fatal damage can be very thin.

Hodgkin's lymphoma is responsible for less than 1% of cancers in Europe. The cure rate in early disease is 98% and in advanced disease tops 85%. End of story. Move on.

Or put it another way. Hodgkin's disease is an unsolved detective story with subplots of mustard gas, sex, fraud and religion; a paradigm for other cancers in research and treatment; a cancer where the cure can be more dangerous than the disease; a story where the final chapter remains to be written.

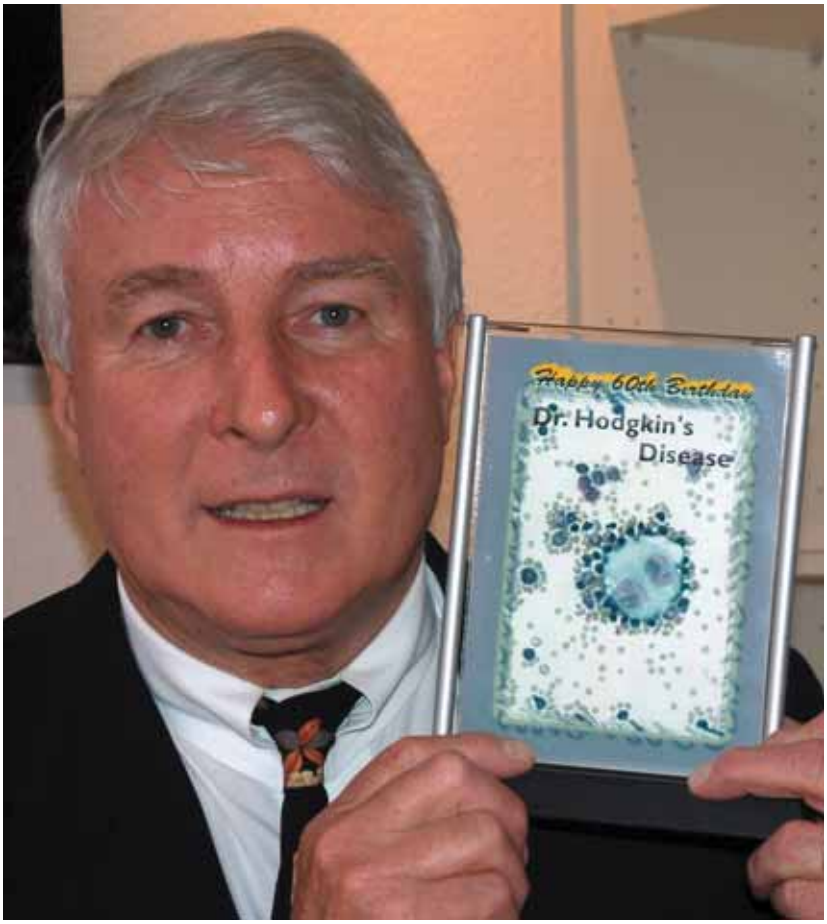
The search for understanding and treatment has inspired doctors and scientists in Europe and America over many decades. In recent years, the torch has been carried by Volker Diehl at the University of Köln, who developed the German Hodgkin Study Group and became known as "Mr Hodgkin's Disease".

As a researcher, Diehl made critical developments in understanding a virus associated with Hodgkin's; as a laboratory craftsman he succeeded in culturing the elusive Reed-Sternberg cell; as a clinician he has improved the treatment of advanced disease. Today, when it is possible to make a successful career studying a single characteristic of a single chromosome, the breadth of his work seems astounding. He is still looking to the future, to reduce the need for cocktails of poisons.

In the 19th century, Thomas Hodgkin carried out post-mortems at Guys Hospital, London, on children and adults who had died following swollen lymph nodes, fever and night sweats. He ruled out tuberculosis and syphilis, but in his 1832 paper, On Some Morbid Appearances of the Absorbent Glands and Spleen, said that on treatment, "I must confess that I have nothing to offer."

About 70 years later, Carl Sternberg and Dorothy Reed described the giant (Reed-Sternberg) cells responsible for Hodgkin's – a disease which, without treatment, has a 95%–98% mortality rate within five years.

Treatment progressed more or less by trial and error, with radiotherapy tried as early as 1902 and nitrogen mustard being tried after doctors noted the effects of mustard gas in World Wars I and II. (In 1943, 80 US sailors



PETER MCINTYRE

Diehl was the first to culture the fragile Reed-Sternberg cell. This certificate, which carries an image of the cell, was presented to him by a group of American pathologists

survived a German bombing attack on their convoy in Bari Harbour, but died later because one of their ships was secretly carrying mustard gas – a banned substance. Autopsies revealed how the gas attacked white cells and lymph tissues.)

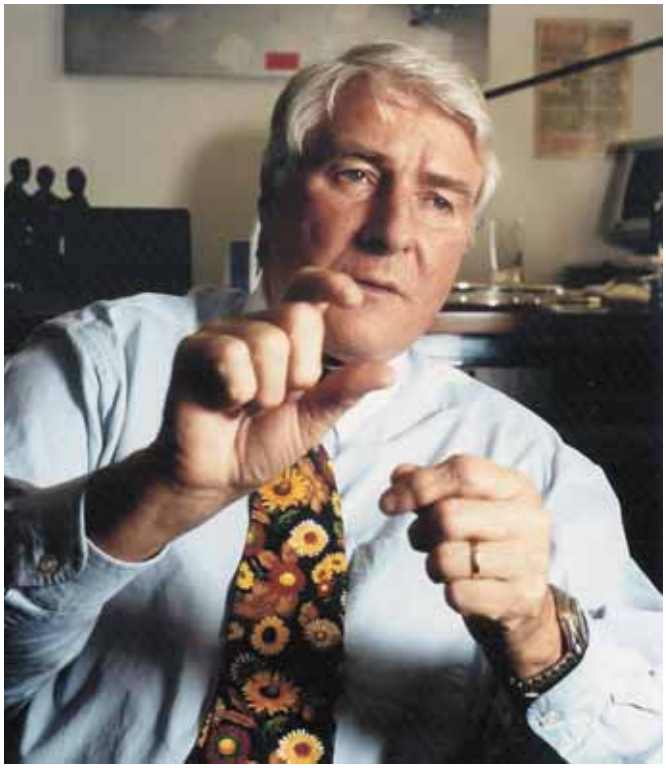
By 1963, Easson and Russell of Christie Hospital, Manchester, England, summed up the hopes of a generation, in a *British Medical Journal* article entitled The Cure of Hodgkin's Disease.

In 1966, fresh from graduation at Freiberg Medical School, Diehl went to Pennsylvania to work with Werner and Gertrude Henle, alongside Harald zur Hausen, another young man destined to make his mark on the world of cancer (see Masterpiece, *Cancer World* issue 7). The Henles, Jews who had escaped from Hitler's Germany, were researching Epstein-Barr virus and recruited these two bright young researchers from Germany to help them. They knew that EB virus was a factor in Burkitt's lymphoma in Africa. Diehl's task was to find out what it did in the US. The Henles were tough bosses. Werner refused to talk to Diehl for six weeks until he learnt a few words of English. Gertrude worked her staff hard and hated it when anyone was off sick.

A METHODICAL SCIENTIST

When a young technician, Elaine Hutkin, failed to arrive one morning, Diehl called her at home and suggested that she drag herself into work. She arrived looking terrible, with a rash, huge lymph nodes, a sore throat, 40 degrees of fever and a yellow colour – the classic

Mononucleosis is known as "kissing disease", and Diehl knew that Elaine had a new boyfriend



symptoms of infectious mononucleosis. Being a compassionate young man, Diehl gave her some medicine and sent her home. Being a methodical scientist, he took a blood sample before she left.

Everyone who worked at the lab had already routinely given blood for tests. Elaine's stood out because she was one of the few who did not have antibodies for Epstein-Barr virus, often a sign of a protected childhood. Five to ten days after her second sample was taken, EB virus cells started to grow. Mononucleosis is known as "kissing disease", and Diehl knew that Elaine had a new boyfriend. He felt certain that she had acquired the EB virus from her boyfriend, and that this had transformed her lymphocytes.

The Henle team contacted Yale – knowing that University doctors routinely took blood samples when students arrived, and asked for samples from all the students who developed mononucleosis, both pre- and post-illness. The results were a tribute to protective parents and to delayed passion. "These were often girls who had an academic mother or father, who were not allowed to go out and play with other children in their local area. Then they came to Yale and met other students and for the first time kissed with an intensive exchange of cells. We got about 40 pre- and post-illness sera, and in five days we knew that all these mononucleosis kids were EB negative beforehand and EB positive after the illness."

Diehl recalls the excitement of the results, showing EB virus as a causative agent in mononucleosis. In 1968, he got a scholarship to Kenya from the US National Cancer Institute (NCI) to see whether patients with Burkitt's lymphoma also showed signs of mononucleosis. This project turned to dust within days of arrival. The mission doctors had never heard of infectious mononucleosis. "I said it is a triad of very heavy tonsillitis, lymphadenopathy, fever and a big spleen and a big liver," and they laughed". At a 5 am clinic, he found hundreds of patients with malaria and hook worm, with enlarged lymph glands, tonsillitis, anaemia, fever and an enlarged spleen. As it turned out, none had mononucleosis, because they'd all been exposed to it at a very early age. The research was over before it began.

"I was very disappointed. I said I wanted to stay in this beautiful country. I told the flying doctor service that I would operate with them if they would help me in what I wanted to do."

He decided to collect sera to see whether people who developed Burkitt's showed a change in their EB virus status. This was a typical Diehl strategy: combining lateral thinking

Diehl's 3,000 serum samples became the basis of the current huge WHO database

"This could only have been a Japanese or Teutonic endeavour," Diehl says, with a hint of self-mockery

with painstaking (some might say, tedious) field-craft. Over the course of a year, he criss-crossed Uganda and Kenya, collecting 3,000 serum samples. This became the first WHO serum collection, the basis of the current huge WHO database, the original samples of which are still used for HIV studies.

The following year, Diehl went to Sweden, arriving for the second time in a country where he spoke not a word of the language. He trained in radiotherapy and chemotherapy (and learned Swedish) at Radiumhemmet and the Karolinska Institute.

Coming across Hodgkin's disease for the first time, he began, like many others, to try to culture the Reed-Sternberg cell, and with the same lack of success. "Once you can get the tumour cell out of the body and put it in a tissue culture, you can study it day or night. This Reed-Sternberg cell is very intelligent, but very fragile, and does not want to be examined; it will die in 20 minutes when you take it out of the body. In the body, it calls feeder cells, small lymphocytes, to protect it from the body's killer cells. But as soon as you put it in a little Petri dish, the culture dies."

In Hanover, he continued to try to culture the cell, focusing on those that looked right – like owl monkey cells, with many nuclei and very large nucleoli. They also had to be monoclonal and aneuploid. In 1978, at the 428th attempt, he succeeded.

"This could only have been a Japanese or Teutonic endeavour," Diehl says, with a hint of self-mockery. "A British or American scientist would never have done it. You needed someone who would do it again and again."

Even today, when there have been maybe a quarter of a million attempts to culture Reed-Sternberg cells, there are only 14 cell lines in the world. Five of these were cultured by Diehl.

Packing his cell line into a basket, Diehl went to show them in America, which greeted him with scepticism. Henry Kaplan at Stanford sent him to John Long at Harvard, who had also cultured the cells. Diehl was made welcome, but when he offered to exchange cell cultures, Long turned evasive. The laboratory was in a mess. He was very busy. Rebuffed, Diehl returned to Germany, just before Long was exposed by an assistant as a fraud. His Reed-Sternberg cells did not just look like owl monkeys; they actually were brown-footed owl monkey cells!

Diehl learnt an early lesson. "I always tell my students; listen to nature and our experiments will tell us whether our hypothesis is right or wrong, but never force nature. I always tried to devise subtle experiments that everyone could follow and repeat. I gave my cells away freely so that other people could repeat and correct what I had published, and in all my life I never had to revoke any findings."

At this stage in the late 1970s, radiotherapy in early (stage 1 & 2) Hodgkin's achieved a cure rate of 70%–80%, while chemotherapy cured 30%–40% of people with late-stage disease. Henry Kaplan's team introduced the first effective chemotherapy regimens and devised a classification system still used to stage Hodgkin's disease, according to the location and number of tumours.

A 14-day regimen of MOPP (mechlorethamine, vincristine (Oncovin), prednisone and procarbazine) was introduced in 1964 by Vince DeVita at the NCI. (Mechlorethamine, the "nitrogen mustard" was later replaced by cyclophosphamide, and MOPP became COPP.) In 1973, Gianni Bonadonna from the Italian National Tumour Institute at Milan introduced ABVD – doxorubicin (Adriamycin), bleomycin, vinblastine, and dacarbazine – as an alternative, and this became the gold standard treatment.

"Randomisation was unknown in Germany, and people said you are treating us like rabbits!"

Clinical trials

Diehl had been impressed by the way that Stanford conducted clinical trials, and when in 1978 the German government set aside money to improve research, Diehl and renowned radiotherapist Karl Musshoff started the first Hodgkin's study in Germany. In the first year, they had just five patients. "Randomisation was unknown in Germany, and people said you are treating us like rabbits! There was a 25% refusal rate by patients and doctors because of randomisation. A politician came from Berlin with her young son and she started to cry. She said she was a practising Catholic and didn't want to interfere with God's work. I said to her 'If you think that God really is sovereign, then he will know exactly into which arm of the trial he puts your son'. Others asked me 'What would you do?' I said that if I knew which of a, b, or c was better, it would be unethical to do the trial."

The arguments seemed to work. The German group is now the largest Hodgkin's study in the world, with 1,600 new patients a year, including 80% of German patients. The refusal rate is below 1%.

Amongst many developments, there have been two headline achievements.

The first, published in the *New England Journal of Medicine* in 1998, was a prognostic scoring system, which identified seven risk factors that make it less likely that a patient would remain free from progression of disease following treatment. With none of these factors, Diehl calculated that 84% of patients would remain disease free. With five or more factors, only 42% of patients would remain disease free.

Diehl and his colleagues also worked on improvements to chemotherapy. In the 1990s, the Köln team introduced a BEACOPP combination of drugs, combining drugs from COPP and ABVD, but replacing vinblastine and dacarbazine with etoposide. The timescale was concentrated, giving doxorubicin (Adriamycin) more frequently. Following publication in the NEJM in June 2003, escalated dosage BEACOPP is becoming the new gold standard to treat advanced disease. Diehl's team reported a 20% better tumour-free survival rate with escalated BEACOPP than with the alternatives. "This means that of 100 young patients 11 survive better with the BEACOPP escalated than with the COPP ABVD."

Although BEACOPP has gained ground, it is still not widely used in the US or in the UK, and an EORTC (European Organisation for Research and Treatment of Cancer) trial is currently comparing this regimen with ABVD in stage 3/4 patients. BEACOPP is not suitable in early-stage Hodgkin's, or in patients older than 60.

The high cure rate for Hodgkin's throws the spotlight onto the adverse effects of treatment – both radiation and chemotherapy. If, after treatment, a patient remains free of disease for 12–15 years, the risks from the after-effects of treatment start to outweigh the risk of death from Hodgkin's.

Extended field radiation used in the 1970s and 1980s raised a young woman's chance of later developing breast cancer by a factor of 90. The radiation dose has been reduced and organs are better shielded, but there are still many radiation-induced problems. Chemotherapy induces leukaemia, non-Hodgkin lymphoma, lung, breast, gastric and thyroid cancers, melanomas and sarcomas of bone and soft tissue. There is also an increased risk of cardiac and pulmonary disease.

Diehl says that balancing benefits and dangers requires not only the right treatment regimen, but also experience in treatment. "Effectiveness and lack of damage – this is always the balance. The therapeutic window is very small.

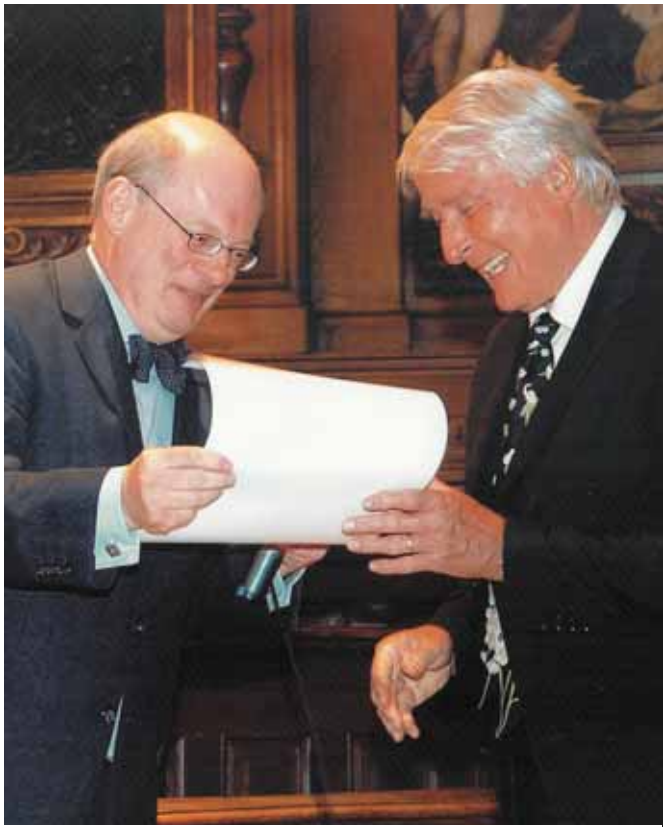
"With ABVD you get 40% regrowth of the tumour. With BEACOPP we get only 10% regrowth of the tumour. But BEACOPP creates infertility in boys in about 90% of cases and induces 1%–2% acute myelocytic leukaemia. Despite this, we still have an 11% higher cure rate after seven years follow-up, including these negative effects. This is the reason why I propose treating only advanced disease with BEACOPP. Early disease we treat with ABVD and radiotherapy.

"BEACOPP is a great poison. It is terrible. I would like to have something better! Sometimes I wake up in the night and ask what will happen to my young patients in 10 to 15 years. These are my nightmares. We propose that you should not treat advanced Hodgkin's disease if you do not have experience with leukaemia or a very aggressive oncology treatment, so you have platelet support and know what to do when you get septicaemia."

Because the cure rate is about 98% in early stages, in many countries Hodgkin's treatment is often in the hands of private doctors rather than cancer centres.

"Everybody wants to treat early disease because it is easy. A young, healthy, beautiful, rich patient says 'I have a lymph node here and I feel a little bit scratchy and I am itchy.' The doctor says 'You may have a virus.' After six weeks when the load has not gone away and the fever comes and goes, he says 'We should do a biopsy.' Then he finds that it is not just a virus, it is Hodgkin's disease. If you find it is stage 1, you give two courses of a very moderate ABVD chemotherapy and a little bit of radiation and you have a 98% cure rate. In an intermediate stage (two lymph nodes) you give four courses of

"Sometimes I wake up in the night and ask what will happen to my young patients in 10 to 15 years"



Receiving an honorary doctorate from the University of Heidelberg in July 2005 from geneticist, Klaus Bartram

ABVD and a little bit of radiation and you have about 89% to 95% cure.

"But if you get another patient who comes with Hodgkin's in the lymph nodes and in the spleen or the liver, he is very sick. If he has a stage 4 disease, he is very sick, has lost 10 kilos and has fever and night sweats. You had better take him to the ward and treat him with BEACOPP escalated, and you had better be very careful.

"When you treat him he really gets sick. BEACOPP is not a soft option. It is quite aggressive, with 2% early death rate due to the treatment if you do not do it right. You have to really know how to do it."

However, Diehl says that doctor-induced deaths have fallen to around 1% of patients, and that the cure rate in advanced disease has risen from 30% three decades ago to 85%–90% today with chemotherapy and radiotherapy.

Although he has high hopes for molecular medicine and targeted treatments, Diehl feels that funding neglects the painstaking clinical research that makes such a difference. "My molecular work was paid millions of euros from the Deutsche Forschungsgemeinschaft (German Research Foundation). We had a world-leading group of 40 people working on molecular research and Hodgkin's disease. I did not cure one patient with that. But we cured many, many patients by our disciplined clinical work with practitioners, the small hospitals and the doctors."

Expertise in the German Study Group is so high that it is bringing a reversal of policy by the German medical insurance companies. "Three years ago, the insurance companies and the government said that if a patient is in a clinical study, insurance money will not pay for it, because this is science, not medicine. This year an insurance company said we want every patient who comes down with Hodgkin's disease to be put into your study – otherwise we won't pay for them. The insurance company said this is a blueprint for all the big killing diseases for lung cancer, and so on."

Unanswered questions

But Hodgkin's still keeps its secrets. Diehl says, "My lifetime is Hodgkin's disease, and I am called Mr Hodgkin's disease, but I still don't know the answers to many questions."

Why, for example, is it the most common lymphoma in young adults in Sweden, but rare in China and Japan? There is clearly a genetic

"We cured many patients by our disciplined clinical work with the small hospitals and the doctors"

predisposition, as shown by a study on concordant twins in the US. But second- or third-generation Chinese in Vancouver or Hawaii have the same risk as the rest of the population, so there is also an environmental factor.

Then there is the strange age profile, with a small number of childhood cases, and then a cluster in the twenties and a second smaller peak between the ages of 50 and 60. Are these diseases the same disease or different? There is also the oddity that Hodgkin's has such a low proportion (1%–2%) of cancer cells in the 'tumour', with the rest made up of fibrous reactive tissue.

And still puzzling, after all these years, is the role of Epstein-Barr virus. Half of Hodgkin's patients have the EB genome in their tumour cells, and the other half don't. But a disproportionate number of patients had mononucleosis in childhood.

Diehl and his friend zur Hausen, the expert in viral links to cancer, discuss this endlessly. Diehl has a theory that the EB virus plays a "hit and run" role, introducing cancer cells which break free before the T-cells kill off the EB virus. "It makes the drop, and is so clever that it loses the virus and the genome has gone and there is no EB virus."

zur Hausen does not agree, saying that if the virus were the cause, it would be found. He and his wife, Ethel-Michele de Villiers, professor of virology at Heidelberg, have suggested a TT virus as a candidate for cases where EB virus is absent. Diehl is sure that molecular science will soon reveal the answers.

Hodgkin's has by no means been Diehl's only work. From 1982 to 2003, he was chair of internal medicine at Köln University, in charge of 120 beds, covering intensive care, nephrology, gastroenterology, rheumatology, immunology, haematology and oncology, as well as teaching 300–400 students. In 2003, he became the

Playing in a string quartet in 1955, during his time in Kenya. Diehl is on the *far left*

founding director of the Heidelberg Comprehensive Cancer Centre, aiming to boost transnational research and working with 15 university departments and several hospitals around the Deutsches Krebsforschungszentrum.

He was involved in the treatment of Russian politicians and the President of Hungary, President Antal. He now teaches for about a week each year in Russia.

He has experience both as a specialist and as a generalist, and when asked which is better, his daunting answer is "both". "I told my students to be a generalist in the phenomenology and the appearance of a disease. Know that when you have a pain in the back it could be a heart attack, it could be a pulmonary embolism or it could be kidney disease. But then when you dig down and get closer to the cause, you have to specialise. I told them never to be a clinician without having had some time in very good research, so that you know about the causes of disease and the pathways of the molecules. I tried to be a broad-minded doctor who knows the differential diagnosis of almost all the internal medicine diseases, but also a deep-rooted scientist who could be a world master in one field."

"I am called Mr Hodgkin's disease, but I still don't know the answers to many questions"

Is radical prostatectomy of benefit in men with localised prostate cancer?

Shomik Sengupta and Horst Zincke*

In men with intermediate- to high-risk prostate cancer, radical prostatectomy has been shown to lower the risk of local or systemic progression, and cancer-specific and overall mortality, compared with watchful waiting.

IN the preceding two decades there has been widespread use of radical prostatectomy (RP) in the treatment of men diagnosed with prostate cancer, as a result of both accumulating surgical expertise and an ongoing shift towards early diagnosis. Despite this, data on the efficacy of RP in controlling prostate cancer have been derived from numerous nonrandomised and generally single-institutional investigations.[1] In some studies, long-term cancer-specific survival rates for patients with clinically localised prostate cancer appear to be similar regardless of initial therapy, thus fuelling speculation on the need for RP.[2]

This active trial (see opposite) reported by the Scandinavian Prostate Cancer Group is based on 695 patients randomly assigned to undergo surgery or watchful waiting between 1989 and 1999, and provides the only high-level evidence of the oncological effectiveness of RP in the treatment of prostate cancer. Earlier reports of this trial had demonstrated improved progression-free and disease-specific survival,[3] with no detriment to quality-of-life[4] among surgically treated patients. With a median follow-up of 8.2 years, the authors extend their previously reported findings. Among men treated with RP, compared with those managed by watchful waiting, the authors observed a further reduction over time in the rates of local progression (10-year cumulative incidence 19.2% vs 44.3%), systemic progression (15.2% vs 25.4%) and death from prostate cancer (9.6% vs 14.9%). In addition, statistically significant benefits of RP in terms of overall mortality (27.0% vs 32.0% at 10 years, P=0.04) and the utilisation of hormonal therapy (110 vs 177 patients at follow-up, P<0.01) are also demonstrated for the first time.

It is crucial, however, to interpret these results in the context of the patient population treated. The patients seen in clinical practice today represent a lower-risk population than this study cohort, where approximately three-quarters of tumours were palpable and serum levels of PSA (prostate-specific antigen) were higher than 10 ng/ml in almost half the patients. Notably, even in this group of patients, the benefits of treatment only emerge gradually, over at least a five- to ten-year timeframe, in keeping with the long natural history of localised prostate cancer.[1,5] Furthermore, on exploratory subgroup analysis, the survival advantage conferred by RP appears greatest among men under the age of 65 years. Taken together, the above data suggest that, for the spectrum of disease studied herein, RP is of benefit to men aged 65 years or less with a life expectancy of at least 10 years.

It is sobering to note that the absolute reduction in mortality is only moderate, and is likely to be even smaller among lower-risk patients. Recently-proposed protocols for active surveillance,[6] which recommend selective delayed curative intervention (based on parameters such as PSA doubling-time), instead of the palliative hormonal therapy on progression, as utilised in the watchful-waiting arm of this trial, might further attenuate the observed

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differences. Additionally, comparative assessments of RP against other therapeutic alternatives, such as external beam or interstitial radiation, are not yet available. As such, therapeutic decision-making by the patient with localised prostate cancer and their treating physicians is likely to remain complex, despite the publication of these results.

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Synopsis

A Bill-Axelson, L Holmberg, M Ruutu et al. (2005) **Radical prostatectomy versus watchful waiting in early prostate cancer.** *N Engl J Med 352:1977–1984*

Background. Preliminary results of a randomised trial comparing radical prostatectomy (RP) with watchful waiting (also known as observation) in early prostate cancer showed that after a mean follow-up of 6.2 years, RP was associated with significant reductions in disease-specific mortality and distant metastases, but had no effect on overall mortality.

Objective. The present study is an updated analysis of the prostate cancer trial, with an additional 3 years of follow-up, to determine whether the decrease in disease-specific death with RP is caused by the reduced incidence of metastasis, and to further investigate the effect of RP on overall survival.

Design and intervention. Men with untreated localised prostate cancer were enrolled in this Scandinavian study between 1989 and 1999. Those aged ≥75 years, or those who had a poorly differentiated tumour, prostate-specific antigen (PSA) level >50 ng/ml, bone scan abnormalities, or a life expectancy of ≤10 years were ineligible. Patients were randomised to RP or surveillance. Hormonal therapy was recommended for local progression or disseminated disease; transurethral resection was recommended for urinary obstruction. Follow-up comprised clinical examinations and blood tests at 6-month intervals during the first 2 years and annually thereafter, plus regular bone scans and chest radiographs. The cause of each death was determined by blinded assessment carried out by an independent panel, and analyses were conducted on an intention-to-treat basis.

Outcome measures. The endpoints were disease-specific death, distant metastasis, local progression, and death from any cause.

Results. Of 695 participants (mean age 64.7 years), 347 were randomised to RP, and 348 were randomised to surveillance. Baseline characteristics for the two groups were similar. Over a median follow-up of 8.2 years, 30 men (8.6%) in the RP group died from prostate cancer, compared with 50 (14.4%) in the surveillance group (P=0.01). There were significantly fewer deaths from any cause in the RP group compared with the surveillance group (83 vs 106, P=0.04). The absolute risk reductions in favour of RP after 5 and 10 years of follow-up increased from 2.0% to 5.3% for disease-specific mortality, giving a relative risk of 0.56 (95% CI 0.36 to 0.88, P=0.01); from 1.7% to 10.2% for distant metastasis, giving a relative risk of 0.60 (95% CI 0.42 to 0.86, P=0.004); from 19.1% to 25.1% for local progression, giving a relative risk of 0.33 (95% CI 0.25 to 0.44, P<0.001); and from 2.0% to 5.0% for deaths from any cause, giving a relative risk of 0.74 (95% CI 0.56 to 0.99, P=0.04). More men managed by watchful waiting underwent hormonal therapy (177 vs 110, P<0.01), palliative radiation (38 vs 29, P=0.30), and laminectomy (4 vs 11, P=0.04). The effect of RP on disease-specific mortality differed according to age, with men <65 years old deriving the most benefit. Disease-specific mortality did not change with PSA level at diagnosis or Gleason score (the sum of grades assigned to the two largest cancerous areas of tissue samples; grades range from 1, least aggressive, to 5, most aggressive).

Conclusions. RP for early prostate cancer reduces disease-specific and overall mortality, and the incidence of metastasis and local progression.

Acknowledgement: The synopsis was written by Sandra Ford, Associate Editor, *Nature Clinical Practice*

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NEWSROUND

Selected press reports compiled by the ESO Cancer Media Centre

Statins do not help protect against breast cancer

→ Journal of Clinical Oncology

Taking statins, the anti-cholesterol drug, does not prevent breast cancer according to a recent meta-analysis of studies, published in the *Journal of Clinical Oncology*.

Statins are a relatively safe group of drugs given to lower cholesterol. They are commonly used in people over 50 years of age to help protect against high cholesterol, which causes heart disease. Recent studies in laboratories have shown that statins may cause breast cancer cells to self-destruct, known as apoptosis. However patient studies have remained unclear as to the benefits of the drug.

The University of Athens looked at seven large randomised trials and nine observational studies published in peer-reviewed journals, and analysed the data. The collaboration found that statin use did not significantly affect breast cancer. Moreover, there was no evidence to suggest that statins have a protective effect against breast cancer. The authors did, however, note that this conclusion is limited by the relatively short follow-up times of the studies analysed. Further studies are required to look at the potential decrease in breast cancer risk among long-term statin users.

■ Use of statins and breast cancer: a meta-analysis of seven randomized clinical trials and nine observational studies. S Bonovas, K Filioussi, N Tsavaris et al. *JCO* 1 December 2005, 23:8606-8612; Can statin therapy reduce the risk of breast cancer? (Editorial). VG Vogel *ibid* pp 8553–8555

Extensive surgery is best option for advanced-stage ovarian cancer patients

→ Mayo Clinic

Researchers from the Mayo Clinic Cancer Center, Rochester, have found that extensive surgery to remove as much cancer as possible through the stomach is the best option for women with ovarian cancer.

William Cliby, a gynaecologic oncologist who headed the study, found that extensive surgery significantly improves survival rates for patients where the cancer has spread the most. The researchers also found that patients undergoing surgery to remove the source of the cancer had a five-year survival rate of 55% versus 28% for those who did not, indicating that extensive surgery aids survival. "This study provides further evidence that surgery to remove as much tumour as possible at the initial operation is the best option for most patients," said Cliby.

The study included 194 women who had undergone surgery for stage 3C ovarian cancer at the Mayo Clinic between 1994 and 1998. In patients with the largest amount of cancer (carcinomatosis), the researchers found that extensive surgery removing the source of the cancer greatly improved the five-year survival rates. "Our study showed a significant survival advantage when a more aggressive surgical approach is used," says Cliby. "Hopefully we'll see increased education and a movement towards a more uniform surgical management of ovarian cancer."

■ Mayo Clinic Cancer Center, Rochester, United States

Chemotherapy treatment for endometrial cancer is more effective than radiotherapy

→ Journal of Clinical Oncology

A new study has shown that giving two chemotherapy drugs to women with endometrial cancer after surgery reduces the risk of the cancer coming back by 29% and increases survival by 32% compared with women who received whole abdominal radiotherapy.

Between 1992 and 2001, researchers from the Gynecologic Oncology Group (GOG) assessed 396 women with an average age of 63. The trial measured patient overall survival and the rate of cancer recurrence. A total of 194 patients with advanced endometrial cancer received doxorubicin and cisplatin for a period of five months following surgery. Another 202 patients received radiotherapy for the whole abdominal area for about one-and-a-half months.

Both patient groups were followed up for just over six years. After five years, 50% of women receiving the chemotherapy drugs were predicted to be alive, compared with 38% of women who received the radiotherapy.

"For the first time, adjuvant chemotherapy has been shown to extend survival in patients with advanced endometrial cancer," said the study's lead author, Marcus Randall, Director of the Leo W. Jenkins Cancer Centre at the Brody School of Medicine at East Carolina University in Greenville, North Carolina. "These findings were surprising, given that previous studies

showed that single chemotherapy agents do not have a significant impact on the disease."

The trial concluded that treatment with chemotherapy significantly improved overall survival for women with endometrial cancer, compared to women treated with whole abdominal radiation.

"This study represents a major advance in the treatment of advanced endometrial cancer," noted Gini Fleming, Director of the Medical Oncology Gynecologic and Breast Cancer Programs at the University of Chicago.

■ Randomized phase III trial of whole-abdominal irradiation versus doxorubicin and cisplatin chemotherapy in advanced endometrial carcinoma: A Gynecologic Oncology Group Study. ME Randall, VL Filiaci, H Muss et al. *JCO* 1 January 2006, 24:36–44; Major progress for a less common cancer. (Editorial) G Fleming *ibid* pp6–8

Fatigue can be a long-term problem for breast cancer survivors

➜ Cancer

More than 30% of breast cancer survivors report problems with fatigue for as long as 10 years after they had been diagnosed with the disease, according to the findings of a recent study conducted at the University of California at Los Angeles. The study found that women suffering from depression or those who had cardiovascular problems were more likely to also suffer from fatigue. Women treated with both radiation and chemotherapy were also more likely to report problems with fatigue.

Julie Bower, one of the study team at the Jonsson Cancer Center, and an assistant professor of psychiatry and bio-behavioural sciences, said: "Fatigue is recognised as one of the most common and distressing side effects of cancer and its treatment. It can significantly impact a woman's quality of life... As survival times for women with early-stage breast cancer lengthen, understanding the long-term effects of cancer and its treatment on functioning and quality-of-life is becoming increasingly important...The study does indicate that fatigue appears to be a persistent problem for a significant number of breast cancer survivors... It also identifies potential targets for intervention, specifically depression and cardiovascular problems, both of which appear to increase risk for persistent fatigue."

■ Fatigue in long-term breast carcinoma survivors: a longitudinal investigation.
JE Bower, PA Ganz, KA Desmond, et al. Cancer, 15 February 2006, 106:751–758

New cervical screening technique is no better than Pap smear test

➜ The Lancet

A new cervical screening technique – liquid-based cytology – being introduced in the UK and the US has been found to be no better than the conventional cervical smear test.

Elizabeth Davey, from the University of Sydney, Australia, and her colleagues, reviewed 56 studies. They concluded that there is no evidence that liquid-based cytology reduced the number of unsatisfactory slides compared to the Pap smear test, nor is there any evidence that it detected more obvious changes in the cells taken from the cervix.

For more than 30 years, screening for cervical cancer has been done using the Pap smear test.

The smear involves the general practitioner or nurse removing cells from the surface of the cervix using a spatula, cotton swab or brush. The cells are placed on a glass slide so that they can be examined under a microscope. As a result of this screening method, incidences of cervical cancer have fallen substantially.

Liquid-based cytology has been developed as an alternative and has been reported to increase the sensitivity of smear tests and decrease the number of slides that aren't good enough to assess for cervical cancer.

According to Davey, "Although we did not find liquid-based cytology to be more accurate than conventional cytology, equivalent performance might be sufficient if liquid-based cytology has other advantages, such as the opportunity for concurrent HPV [human papilloma virus] DNA testing, or reduced reading times, or is more economical than conventional cytology."

■ Effect of study design and quality on unsatisfactory rates, cytology classifications, and accuracy in liquid-based versus conventional cervical cytology: a systematic review. E Davey, A Barratt, L Irwig et al. *The Lancet* 14 January 2006, 367:122–132

Older women are given less of a chance to survive breast cancer

➜ PLoS Medicine

Women aged between 70 and 84 have a 13% lower chance of surviving their breast cancer, according to researchers from Sweden who did a population-based study in one health-care region.

The study, led by Sonja Eaker from the University of Uppsala, looked at 9,059 women between the ages of 50 and 84 who had been diagnosed with primary breast cancer between 1992 and 2002.

The five-year relative survival ratio was estimated for patients classified by age group, diagnostic activity, tumour characteristics, and treatment.

Big differences were found between the management of the cancer according to age.

Older women had larger tumours and fewer lymph nodes examined, and did not receive chemotherapy or radiotherapy as often as the younger group of women did.

The study concluded that less diagnostic activity, less aggressive treatment, and later diagnosis in older women are associated with poorer survival, and that the large differences in treatment of older women are difficult to explain by co-morbidity alone.

Older women suffer from not having their cancer identified adequately and having less invasive surgery. Eduardo Franco from McGill University asks: "To what extent do we as a society want to continue to assign lesser importance to our elderly when formulating health policies and research priorities?"

■ Differences in the management of older women influence breast cancer survival: Results from a population-based database in Sweden. S Eaker, PW Dickman, L Bergkvist et al. *PLoS Med* 17 January 2006, 3(3): e25; Epidemiology as a tool to reveal inequalities in breast cancer care. EL Franco *ibid*, e48

Towards more accurate estimations of survival in terminal cancer

→ British Journal of Cancer

People affected by cancer want to know how long they have to live. Unfortunately, oncologists have trouble estimating and talking about their patients' survival.

A study published in the *British Journal of Cancer* investigated the estimations made by oncologists for newly referred patients with incurable cancer. A total of 102 patients were involved and followed for three years. Oncologists were asked how long each patient would survive, and they were also asked how long 90%, 50% and 10% of similar patients would survive – representing the worst case, predicted and best case scenarios.

Oncologists' estimations of the 90%, 50% and 10% values were fairly accurate. However, their estimations for the majority of their patients were wrong. Only 29% were within 0.67–1.33 times the patient's actual survival, 35% were too optimistic (>1.33 times the actual survival), and 39% were too pessimistic (<0.67 times the actual survival). The proportions of patients with actual survival times bounded by simple multiples of their predicted survival were as follows: 61% between half to double their predicted, 6% at least three to four times their predicted, and 4% no more than one-sixth of their predicted survival.

The authors conclude that the most appropriate way to inform newly referred patients with incurable cancer about their prognosis and the uncertainty surrounding their prognosis is to use the above ranges, based on simple multiples of the predicted survival time.

■ Disarming the guarded prognosis: predicting survival in newly referred patients with incurable cancer. MR Stockler, MHN Tattersall, MJ Boyer et al. *Br J Can* 30 January 2006, 94:208–212

Chemotherapy directly into the abdomen improves survival in ovarian cancer

→ New England Journal of Medicine

Results from a trial conducted at the Johns Hopkins Kimmel Cancer Center, Baltimore, USA, found that women who received chemotherapy directly into their abdomen lived up to one-and-a-half years longer than women who were given traditional, intravenous chemotherapy. There is still no screening test for ovarian cancer, so often the cancer progresses unnoticed. The standard treatment for advanced ovarian cancer is to have surgery to remove the tumour, followed by combined chemotherapy drugs injected into a vein to enter the blood stream. In the first conclusive trial, the Gynecologic Oncology Group (GOG) compared 415 women. One group of 210 women was given a combined chemotherapy treatment intravenously for 24 hours, the other group – 205 women – received the combined chemotherapy intravenously plus a slightly lower amount of chemotherapy directly into the abdominal area. Both of these treatments were given every three weeks for six cycles, and the results were followed up for just over four years.

Patients who received the chemotherapy drugs directly into the abdominal area increased their median survival by 25% compared to patients receiving the standard treatment. Doctors can give larger doses of the drugs when administering them directly into the abdomen, providing better results.

The study was welcomed by Gordon McVie, of the European Institute of Oncology in Milan. "This result vindicates the work of several European groups which have showed unequivocal complete remissions in small cancers in the abdomen, after treatment with intraperitoneal drugs. These results were achieved after intravenous chemo had failed, and were accompanied with long remissions. The technical difficulties, local complications and lack of a randomised trial delayed uptake of this form of therapy for 20 years. Now advances in technology should cut the problems for the patient, and offer real survival prolongation to suitable patients.

"These results will influence clinical practice. It will now be possible for doctors to discuss this way of giving chemotherapy with selected women who are newly diagnosed with ovarian cancer. The data from the GOG trial establishes this method of giving chemotherapy as an important advance in the treatment of ovarian cancer."

■ Intraperitoneal chemotherapy comes of age. SA Cannistra. *N Engl J Med* 5 January 2006, 354:77–79

When clinical trials are compromised

A perspective from a patient advocate

➜ Musa Mayer*

Advocates for early access to unproven treatments may believe they are helping patients, but their actions can put current patients at risk and deny future patients the knowledge they need to make evidence-based treatment decisions, argues **Musa Mayer**.

Twelve years ago, a friend from my breast cancer support group went to court because her insurance company had refused coverage for a bone marrow transplant. Her first transplant had failed and her cancer was progressing again. The insurance company refused coverage for the second transplant on the basis that it was an experimental treatment. The judge, a cancer survivor himself, was clearly moved by her appeal, and my friend got her transplant. Six months later, she was dead – not from her metastatic breast cancer, but from treatment-induced damage to her bone marrow.

Then, a second friend with breast cancer died following her transplant a few months after that, and I began to read the research for myself and to piece together what the studies actually showed – and what they didn't show. My education about clinical trials had begun, as I have previously described in a 2003 essay entitled, "From Access to Evidence: An Advocate's Journey"[1].

It took me some time, and a lot of study, to understand the dynamics of what had actually happened in America with bone marrow transplants in breast cancer. And how wishful thinking on the part of patients and oncologists, public pressure, heart-wrenching media stories of desperately ill young mothers, political and legislative mandates for insurance coverage, personal reputations of researchers, and profit margins of hospitals with transplant beds to fill all managed to widely promote a toxic and expensive treatment before there was sufficient evidence of its safety or efficacy.

The rush to embrace an unproven treatment

Hindsight being what it is, we can appreciate the dynamics now, and see how the uncritical adoption of this treatment off trial added years to the time that it took to enrol individuals in the randomised trials that ultimately would answer the question of efficacy. By the end of

*Musa Mayer is a cancer survivor, advocate, and author of three books on breast cancer

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the decade, in fact, more than 20,000 American women had endured this treatment for no compelling reason. Many died because of it, while others were left with serious and long-lasting side effects.

Of course these women were very ill to begin with, and the prevailing wisdom of the time was that desperate circumstances called for desperate measures. Giving doses of chemotherapy so high that the bone marrow was destroyed, then rescuing the patient with her own stem cells or bone marrow – this treatment had intuitive drama and appeal. Many women at the time, including both of my friends mentioned in the introduction, vowed to "go out fighting," rather than have the longer life and gentler death that might have been theirs with conventional treatment. "If I die," young women would frequently say, "I want my children to know I did everything I could." One transplant unit actually used this coercive argument as a marketing ploy.

Naïvely, I believed until then that doctors could be trusted to rely on good evidence, especially for a treatment as toxic and costly as this one. Certainly, they would never allow themselves to be misled by partial evidence or a compelling theory – that more is better, or that dramatic tumour response in uncontrolled phase II trials of the high-dose regimens actually predicted for clinical benefit. Or, even more shocking, that one existing small randomised trial that many questioned as flawed – and which later, in fact, turned out to have been falsified – would be held up to patients as good evidence for the treatment[2-5].

Looking back now, I can trace my radicalisation as a patient advocate, and my interest in the proper conduct of randomised clinical trials, to the troubling discovery that in the case of bone marrow transplant in patients with breast cancer, the tools of science had been subverted by the rush to embrace an unproven treatment. The fact that this could happen was profoundly disillusioning. I was disappointed with oncologists, but more disturbing to me was the role that many advocates had played in guaranteeing broad access to bone marrow transplants, effectively sabotaging enrolment in the randomised trials that would have

provided a definitive answer years sooner, saving many lives and much personal suffering, not to mention huge financial expenses.

Three years ago, I recounted this story at the Annual Advocacy Training Conference of the National Breast Cancer Coalition (NBCC). Since the bone marrow transplant stampede ended in 1999, many women diagnosed with breast cancer more recently were unaware of what had happened during the 1990s, and that the new mantra of 'targeted therapy' had only recently replaced the 'more is better' model.

The transplant debacle also stiffened the resolve and long-time commitment to evidence-based medicine and research standards held by the NBCC, a grassroots lobbying and advocacy-training organisation committed to the eradication of breast cancer. Standing alone among breast cancer organisations, NBCC had refused to fight for access to a treatment that was still unproven. Their position paper on bone marrow transplant was perceived by many as rigid and uncaring. Yet NBCC's unwavering commitment to the evidence and to the need for trials prior to widespread adoption of the treatment ultimately won them the respect they deserved.

Musa Mayer: Many trained advocates are just as concerned as health professionals are with getting the very best evidence from clinical trials. We can help

What I learned about clinical trials

Tragedies can sometimes be instructive. As an advocate, I learnt a memorable lesson about how clinical trials can go terribly awry through the premature adoption of an unproven therapy. This extraordinarily painful example taught me – and many breast cancer advocates – a great deal about clinical trials: the limitations of phase II studies, the crucial role of randomisation and control groups, the perils of selection bias and stage migration, and surrogate endpoints, such as tumour response, that fail to predict clinical benefit. I also learnt how incredibly important it is to preserve the integrity of clinical trials for patients now and in the future. It is a matter of life and death.

In the years since, the conduct of randomised clinical trials has often been in jeopardy. What prompted me to recount this dark chapter in our history to the NBCC advocates were the current legal activities of an organisation known as the Abigail Alliance (http://abigail-alliance.org). Founded by surviving family members of patients with cancer who had been unable to get access to experimental treatments under development, with support by antiregulatory forces in Washington, DC, the Abigail Alliance first brought a citizen's petition and then a lawsuit against the United States Food and Drug Administration (FDA). They claimed that current restrictions on experimental treatments represented an infringement on the civil rights of dying patients. They proposed a regulation permitting the marketing of experimental treatments after phase I trials to patients who had no other treatment alternatives, claiming that this would in no way interfere with the conduct of confirmatory trials.**

They were firmly convinced that their loved ones could have been saved, if only they had been permitted access. To them – as to me a decade earlier, before I understood what was at stake – the benefit from these cutting-edge treatments was obvious. The need was urgent. People they loved were dying. New treatments had been developed. How could anyone be cruel enough to deny a patient the next new treatment that might save or extend life? Randomised trials were seen as not only unnecessary but ethically indefensible. To them, the notion of equipoise was simply an absurdity. Strong perceptions of drug efficacy, nurtured by pharmaceutical industry advertising, kept hope alive.

At first, the Abigail Alliance initiative to market drugs after phase I trials seemed so absurd that many of us advocates didn't take it

**In November, 2005, legislation supporting this position was introduced in the US Senate.
U.S. Senate Bill S.1956 "Access, Compassion, Care, and Ethics for Seriously Ill Patients Act" http://thomas.loc.gov/cgi-bin/bdquery/z?d109:s.01956:

seriously, and took no action. But the Alliance was very serious and very determined. Publicised with the smiling face of their founder's deceased daughter, Abigail, this group acquired considerable media attention, appearing on NBC's Today Show and inspiring a *Wall Street Journal* editorial with the memorable title: FDA to Patients: Drop Dead[6].

Of course, the first wave of activism for early access to treatments had come from AIDS advocates, giving rise to 'accelerated approval', or Subpart H regulations, in 1993, which permitted drugs to reach the market early in the case of life-threatening illnesses for which no other treatment existed. These approvals could be based on surrogate endpoints in uncontrolled trials, with the provision that clinical benefit must ultimately be shown in post-marketing randomised, controlled studies. In the intervening years, many cancer drugs have been approved in this way.

Meanwhile my own understanding of issues in clinical trials continued to evolve. Since my work focuses on women with metastatic breast cancer, my keen interest in drug development and clinical research led to my becoming a Patient Representative and Consultant in the FDA's Cancer Drug Development Program.

Accelerated approval of cancer drugs

In September 2002, the Oncologic Drugs Advisory Committee recommended accelerated approval of AstraZeneca's drug gefitinib (Iressa), based on a 10% tumour response rate in late-stage non-small-cell lung cancer[7-9], despite concurrent negative findings in large randomised controlled trials[10,11]. It was a heated, emotional meeting, with many patients who otherwise would not have been alive offering personal testimony of benefit from the drug. Obviously, some drug effect was present in this small minority of patients. Many others present, however, were disturbed by the precedent set by the vote for approval, with the actual evidence showing tumour response in only 20 patients in two small phase II trials. Other people wondered why no target had been found for this 'targeted' therapy to better predict response and non-response, as it had for trastuzumab (Herceptin) and hormonal therapies in breast cancer.

The FDA held an Oncologic Drugs Advisory Committee meeting the following spring, at which we reviewed seven cancer drugs for eight indications that had been granted accelerated approval, but had failed to complete the confirmatory trials. Avoiding the problem that many drugs given accelerated approval had had enrolling individuals in their trials once the drug was on the market, AstraZeneca agreed to complete its confirmatory trial of gefitinib overseas. But ultimately, gefitinib failed to show a benefit in the large mandatory confirmatory "Iressa survival evaluation in lung cancer" trial[12-15].

Meanwhile, independent researchers had managed to identify the epidermal growth factor receptor mutation that selects for most of the 10% of patients with lung cancer who respond to the drug[16-18]. Then in November 2004, Genentech's competing epidermal growth factor receptor inhibitor, erlotinib (Tarceva), secured full FDA approval. In the face of the failed confirmatory trial for gefitinib, FDA effectively removed the drug from the market, while allowing patients already responding to gefitinib to continue with their treatment. Among many other issues, the story of gefitinib in lung cancer illustrates the pressing need for concurrent development of biomarkers that select for treatment response to targeted therapies.

Early access to treatments and the impact on clinical trials is, of course, only one of the many important issues with clinical trials that could be addressed, but I've emphasised it here because it represents an arena that has engaged

Patients facing treatment decisions in the future are rarely served by stopping clinical trials early

the patients and the public so consistently during my years as an advocate.

Early closure of trials

Earlier this year, I spoke at the annual meeting of the American Society for Clinical Oncology on a related issue – the ethical and clinical dilemmas relating to the early closure of clinical trials in breast cancer. Such early closure has occurred with increasing frequency in recent years, notably in the P-1 breast cancer tamoxifen prevention trial[19], the MA-17 trial of letrozole (Femara) after tamoxifen[20], and most recently, the adjuvant trastuzumab (Herceptin) trials[21].

The issue of early trial closure is similar to that of accelerated approval of an experimental drug – in both cases, the balance of immediate needs for patients being treated today must be weighed against the knowledge gained that will advance evidence-based medicine and help patients in the future. Patients facing treatment decisions in the future, after mature results of clinical trials have been published, clearly benefit most from the completion of well-designed randomised trials with meaningful endpoints and long periods of follow-up. Their needs are rarely served by stopping clinical trials early, or by trial designs that do not randomise trial participants, examine toxicity carefully, look at overall survival, or follow-up with patients to pick up any unanticipated late-term effects.

Evidence-based patient advocacy

It has been important for us as advocates to speak out on these issues in every available forum, as individuals and as organisations. Speaking out in this way educates the public as well as the medical and research communities. In my 2003 essay[1], I defined 'access advocates' as those who see their role as arguing, as Abigail Alliance does, for earliest access, regardless of the effect on clinical research.

When I wrote that 2003 essay, I wanted health professionals to know that the perception of advocates clamouring for early access and compromising clinical trials is far from a complete picture. Many trained advocates are just as concerned as health professionals are with getting the very best evidence from clinical trials. We can help. Our stories have the power to move the public, to influence policy and legislation, and to help enrol patients in trials that they will want to be part of. I believe trained evidence-based advocates should have a seat and a voice at every table where clinical trials are designed and implemented. Together with scientists and clinicians, we can help health professionals to define the most meaningful questions, and ensure that the design and conduct of trials are everything they should be. And we can help to educate the public about the need for well-designed, properly implemented clinical trials.

As a writer, I understand the power of stories. Stories humanise policy, and offer the personal context in which policies and positions actually matter to people. Without our human stories to illustrate and elucidate cause and meaning, the positions health professionals take will not be very meaningful to the public and to the patients they hope to enrol in clinical trials. Properly told, stories have the power to move people, to change minds and hearts. Potentially, they have the power to reach a public who has little understanding of the research enterprise, and barely grasps the need for clinical trials. Everyone is touched by illness. Everyone requires evidence-based health care. I think we need to stop allowing the public dialogue on clinical research to be controlled by the drug companies and by mass media. We need to tell these important stories and express our strong convictions.

My work as an advocate and my personal experience with NBCC tells me that policy positions are important, and that we can have an influence if we are willing to stand up for our principles. Consistent, well-reasoned evidence-based positions command respect, if not always agreement. So does steadfast refusal to take the expedient position, even when it may be more popular. These are the hallmarks of what can only be called integrity.

References: Details of all references cited in this article can be found at www.cancerworld.org/cancerworld

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A trial of strength

Can industry resist the growing demands for greater transparency?

Peter McIntyre

Patients, doctors, academic researchers and the World Health Organization all want industry to be a lot more open about the drugs they are trialling. The industry is pleading commercial confidentiality. The two sides are locked in an argument over the requirements of a proposed WHO clinical trials registry. The question is: who will blink first?

Patients and doctors hope to gain unprecedented access to information about clinical trials through a one-stop global search engine. A World Health Organization initiative, now under discussion, would allow patients with cancer and other critical conditions to search for trials about promising lines of treatment. It would also bring a more comprehensive and faster approach to making the outcomes of clinical trials public.

WHO looks set to win broad agreement for a 20-item registration data set about trials, including details of products or procedures, the exact aims of the trial and the outcome (see pp. 64,65). Later this year, WHO plans to give every trial a Universal Trial Reference Number (UTRN) and to launch a search engine that will trawl more than 50 clinical trials registries worldwide.

The European Cancer Patient Coalition (ECPC) has welcomed the WHO International Clinical Trials Registry Platform, saying that innovative trials are the last hope for some patients, but that information is often shrouded in a veil of secrecy.

However, the scheme will fall short of full disclosure and may exclude phase I/II 'exploratory' trials. The pharmaceutical industry is also insisting on an option to delay disclosing information about what it deems to be commercially sensitive, including the name of some drugs or even the aim of a trial.

There is a stand-off between the WHO and the industry as to the extent of any exclusions, the length of any delay and who would have access to the information on a confidential basis.

Campaigners say that the commercial case for secrecy is weak, since information can already be found on the Internet by those who know where to look.

A 20-year campaign for more information was given teeth after a series of high-profile scandals. In 2003, the New York Attorney General started civil action against GlaxoSmithKline over reports of suicidal feelings in children and adults taking the anti-depressant Seroxat (paroxetine). In 2004, Merck & Co. (USA) withdrew the anti-inflammatory drug Vioxx (rofecoxib) due to concerns about the raised risk of heart attacks and other cardiovascular events.

MARY GODLESKI / STAR LEDGER / 1009

In January 2005, four pharmaceutical associations and federations covering Europe, America and Japan* issued a joint statement saying: "We recognize that there are important public health benefits associated with making clinical trial information more widely available to healthcare practitioners, patients and others. Such disclosure, however, must maintain protections for individual privacy, intellectual property and contract rights, as well as conform to the regulations in relevant countries."

Exploratory trials

The statement committed the industry to register all clinical trials *other than exploratory trials* (our emphasis) within 21 days of starting patient enrolments. Information would include that "sufficient to inform interested subjects (and their healthcare practitioners) how to enrol". The industry proposed putting other information into a secure database accessible by medical journals on a confidential basis.

Under their plans, trial results would be disclosed only when a drug is commercially available in at least one country. Exploratory trials would be disclosed, "if they are deemed to have significant medical importance and may have an impact on a marketed product's labelling." In the case of failed trials, "study sponsors are encouraged to post the results if possible," but only if results have "significant medical importance".

Although the joint statement represented a shift on the part of the industry, in the eyes of many outsiders it did not go nearly far enough, and it left all the critical judgements about what to release in the hands of the trial sponsors.

The International Committee of Medical Journal Editors (ICMJE) got tough. The editors declared that, from 13 September 2005, they would not publish results from trials unless

* The four pharmaceutical bodies are the European Federation of Pharmaceutical Industries and Associations (EFPIA), the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), the Japanese Pharmaceutical Manufacturers Association (JPMA), and the Pharmaceutical Research and Manufacturers of America (PhRMA)

they were registered before any patients were recruited.

The ICMJE policy embraces the *New England Journal of Medicine*, the *Lancet* and other leading medical journals, and the effect was seismic. As researchers rushed to beat the deadline, there was a 73% increase in the number of clinical trials registered on ClinicalTrials.gov, compiled by the US National Institutes of Health and the US National Library of Medicine. However, ClinicalTrials.gov holds few European phase I/II cancer treatment trials among its 33,000 records.

The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), which represents research-based pharmaceutical, biotechnology and vaccine companies, launched its own clinical trials portal in September 2005, to link online information from the pharmaceutical industry worldwide.

IFPMA chairman, Daniel Vasella, also chairman and CEO of Novartis, said the portal showed the industry's "commitment to full transparency in the interest of patients and healthcare professionals." However, IFPMA argued that they should be able to delay publication of five "sensitive items", including the scientific title of the study, the intervention itself (such as the name of the drug), the target sample size and the key primary and secondary outcomes.

What this means in practice was demonstrated when Deborah Zarin, Director of ClincialTrials.gov, investigated what was actually filled in by companies on her register. She reported in the *New England Journal of Medicine* in December 2005, that in May 2005, 10% of entries gave no information about the drug being tested. Three industry giants, Merck (USA), GlaxoSmithKline and Pfizer, used a non-specific term such as "investigational drug" between 29% and 91% of the time.

Zarin concluded that an optional register would not work. "When trial sponsors have the option of providing information of marginal clinical value in a particular data field, our findings show that some companies provide useful information and others do not."

Pressure from the editors substantially improved the quality of information. In May 2005, Merck used a non-specific entry such as "investigational drug" for 120 out of 132 trials registered. In October 2005, it provided the name of the drug for all 52 new trials and retrospectively added the name for all but one existing trial. However, GlaxoSmithKline still registered 20% of its trials with a non-specific entry, while Pfizer withheld the drug name for 10% of its trials.

A similar story was revealed for "primary outcome measure" which was commonly left blank by industry before 20 May 2005. Since then, three-quarters (76%) of industry records include an entry.

In September 2005, the four industry groups broadly adopted the WHO registration data set, but continued to argue that information about the five "sensitive" items could be delayed until the drug won approval. Other important areas of disagreement include the timing of when trials should be registered, the role of ethics committees, and the proposal for a WHO unique trial number, which the IFPMA says is unnecessary and bureaucratic. WHO says that the existing system has led to trials being reported twice and double-counted during meta-analysis.

Full disclosure

WHO is challenging critics to spell out exactly what they have to lose by full disclosure, and asks how delayed disclosure is compatible with maintaining public trust. It has launched an open forum on its website, asking for precise examples of how commercial confidentiality or

As researchers rushed to beat the deadline, there was a 73% increase in clinical trials registered

WHO is challenging critics to spell out exactly what they have to lose by full disclosure

intellectual property rights could be damaged (www.who.int/ictrp/comments4/en/). WHO says that the registration of all trials – including early- and late-phase trials – is "a scientific, ethical, and moral responsibility".

It adds, "The Registry Platform also considers it critical on scientific grounds, and in the public interest, that all 20 items in the Registration Data Set be fully disclosed at the time of registration."

WHO will also organise a public forum on delayed disclosure when the Scientific Advisory Group meets in Geneva on 26–28 April.

However, WHO does concede that academic and commercial concerns might justify delaying disclosure, saying, "the issue currently open for discussion is the timing of disclosure, not whether to disclose." It seems that WHO may go along with delaying disclosure of some information for six months or a year.

Ida Sim, WHO project co-ordinator, said: "Many people in the pharmaceutical industry say that disclosure is the right thing to do. It is not just better for patients, it is also better for the industry. If information is available then their products are more useful.

"We might not get complete openness at first, but we can always extend and review the policy. But our first policy statement has to have scientific and ethical integrity or we have lost the game, because this is about restoring public trust."

Beat Widler, global head of clinical quality assurance for Roche, said that the company will include all 20 WHO elements by March 2006. "We have always given the name of the investigational product. We agreed with some of the critics that it does not make sense to write 'investigation drug', because that hides the purpose of the whole exercise."

However, he criticised lack of clear aims for registration and what he saw as the exclusion of the industry from day-to-day discussions within WHO.

"We need to have absolute clarity about the intentions and the goals of these registries. There is a lot of confusion in the public domain, and also amongst the journal editors to be quite frank. The original intention was to provide early access to novel therapies for patients in life-threatening conditions. It has evolved into a much more general discussion about transparency and it is not clear what kind of transparency we mean.

"I am personally involved in the IFPMA working group that is very actively involved with the development of the [IFPMA] search portal, but nobody from this group has been officially invited to participate in the WHO working group, although we have asked many times. It is a pity that people in the industry who have the knowledge and developed a genuine interest in promoting transparency have been sidelined. We need to bring all the people who want to find solutions around the table, and not limit it to groups who frankly have their own political agenda."

Iain Chalmers, a member of the WHO Advisory Board for the International Clinical Trials Registry Platform, and editor of the James Lind Library, believes that complete openness is the only way to regain public trust. "The reputation of the industry is lousy at the moment. People regard it as behaving as disgracefully as the tobacco industry. But there are people in the industry pushing for unlimited openness right from phase I. This is the only way to restore public confidence. Change is inevitable, but it will only happen fully if the journals and the research ethics committees insist on it. The WHO can try to persuade, but it has not got the muscle to ensure it happens."

Chalmers also called for a reduction in the number of repetitive and unnecessary trials.

"I want to see systematic reviews of data to show that existing trials are still necessary. There is an awful lot of indefensible redundancy in clinical research, driven by marketing and because people are too lazy to check what has already been done."

Final option

The European Cancer Patient Coalition points out that exploratory trials for cancer treatment are on patients who have run out of options, not on healthy volunteers. In its submission to the WHO debate, ECPC says, "For many patients, participation in a phase I trial might be their last option to stay alive. This is why access to information about early clinical trials is of critical importance to cancer patients, in stark contrast to patients with other chronic diseases.

"Patients face considerable barriers when

Proposed data set for the WHO clinical trials registry

1. **Primary Register and Trial ID #.** Select name of Member Register in which this trial was first registered (the trial's "Primary Register"), and that register's register-specific unique ID assigned to this trial
2. **Date of Registration in Primary Register.** Date when trial was officially registered in the Primary Register DD/MM/YYYY
3. **Secondary ID#s.** Other identifying numbers and issuing authorities besides the Primary Register, if any. Include the sponsor name and sponsor-issued trial number (e.g., protocol number) if available. Also include other member and non-member trial registers that have issued a number to this trial. There is no limit on the number of Secondary ID numbers that can be provided
4. **Source(s) of Monetary or Material Support.** Major source(s) of monetary or material support for the trial (e.g., funding agency, foundation, company)
5. **Primary Sponsor.** The individual, organisation, group or other legal person taking on responsibility for securing the arrangements to initiate and/or manage a study (including arrangements to ensure that the design of the study meets appropriate standards and to ensure appropriate conduct and reporting). The Primary Sponsor is normally the main applicant for regulatory authorisation to begin the study. It may or may not be the main funder
6. **Secondary Sponsor(s).** Additional individuals, organisations or other legal persons, if any, that have agreed with the Primary Sponsor to take on responsibilities of sponsorship.
   A Secondary Sponsor may have agreed:
   - to take on all the responsibilities of sponsorship jointly with the Primary Sponsor; or
   - to form a group with the Primary Sponsor in which the responsibilities of sponsorship are allocated among the members of the group; or
   - to act as the Sponsor's legal representative in relation to some or all of the trial sites; or
   - to take responsibility for the accuracy of trial registration information submitted
7. **Contact for Public Queries.** e-mail address, telephone number, or address of the contact who will respond to general queries, including information about current recruitment status
8. **Contact for Scientific Queries.** e-mail address, telephone number, or address, and affiliation of the person to contact for scientific inquiries about the trial (e.g., principal investigator, medical director for the study at the sponsor). For a multi-centre study, enter the contact information for the lead Principal Investigator or overall medical director
9. **Public Title.** Title of the study intended for the lay public in easily understood language
10. **Scientific Title.** Scientific title of the study as it appears in the protocol submitted for funding and ethical review. Include trial acronym if available
11. **Countries of Recruitment.** The countries from which participants will be, are planned to be, or have been recruited
12. **Health Condition(s) or Problem(s) Studied.** Primary health condition(s) or problem(s) studied (e.g., depression, breast cancer, medication error)
13. **Intervention(s).** Enter the specific name of the intervention(s) and the comparator/control(s) being studied. Be sure

attempting to find out about clinical trials in progress. Some doctors will not tell their patients about clinical trials … because they are convinced that the treatment they prescribe is superior to trials, or because they are not well informed about ongoing trials themselves."

ECPC is calling for easy-to-understand information about phase 1 trials on patients, even if this was limited to title, rationale, condition, intervention, brief description of study and expected outcomes.

Jan, who runs Leukämie-online (www.leukaemie-online.de) for leukaemia patients in German-speaking countries, found out at the age of 28, that he had chronic myeloid leukaemia (CML).

He believes his life was saved by an "investigatory" trial.

to describe the intervention(s) for every arm of the study in separate entries. Use the International Non-Proprietary Name if possible (not brand/trade names). For an unregistered drug, the generic name, chemical name, or company serial number is acceptable. If the intervention consists of several separate treatments, list them all in one line separated by commas (e.g., "low-fat diet, exercise")

The comparator/control intervention is/are the intervention(s) against which the study intervention is evaluated (e.g., placebo, no treatment, active control). If an active control is used, enter the name(s) of that intervention, or enter "placebo" or "no treatment" as applicable.

For each intervention, describe other intervention details as applicable (e.g., dose, duration, mode of administration, etc.)

14. Key Inclusion and Exclusion Criteria. Key inclusion and exclusion criteria for participant selection, including age and sex

15. Study Type. A single group study is one in which all participants are given the same intervention. Trials in which participants are assigned to receiving one of two or more interventions are NOT single group studies. Crossover trials are NOT single group studies.

For multiple group studies (two or more study groups), a trial is "randomized" if participants are/were assigned to intervention groups by a method based on chance

16. Date of First Enrolment. Anticipated or actual date of enrolment of the first participant (MM/YYYY)

17. Target Sample Size. Number of participants that this trial plans to or had planned to enroll

18. Recruitment Status. Recruitment status of this trial

- Pending: participants are not yet being recruited or enrolled at any site
- Active: participants are currently being recruited and enrolled
- Temporary halt: there is a temporary halt in recruitment and enrollment
- Closed: participants are no longer being recruited or enrolled

19. Primary Outcome(s). Outcomes are events or experiences that trial investigators measure because it is believed that they may be influenced by the intervention or exposure. The Primary Outcome should be the outcome used in sample size calculations, or the main outcome(s) used to determine the effect of the intervention(s).

Enter the names of all primary outcomes of the trial. Be as specific as possible (e.g., "Beck depression score" rather than just "depression"). For each outcome, also provide all the timepoints at which it is to be measured. Examples: Outcome name: all cause mortality, Timepoint: one year; or Outcome name: Beck depression score, Timepoint: 6, 12, and 18 weeks

20. Key Secondary Outcomes. Outcomes are events or experiences that trial investigators measure because it is believed that they may be influenced by the intervention or exposure. Secondary outcomes are events or experiences other than the primary outcome(s) that will be used to evaluate the intervention(s), and that are specified in the study protocol.

Enter the name of each secondary outcome of the trial. Also provide all the timepoints at which this outcome is to be measured. Examples: Outcome name: cardiovascular mortality, Timepoint: 6 months; or Outcome name: functional status, Timepoint: 4 and 8 weeks

"I went onto the Internet and there was a US group of patients having a discussion on Yahoo. I went from doctor to doctor to get different opinions and evaluate options." After a doctor from Mannheim spent more than an hour on the phone explaining his options, Jan joined a 20-patient phase I/II trial combining imatinib (Glivec, then known only as STI-571) with pegylated interferon-alpha. Five years later he is in complete remission.

"If phase I is excluded, I would be disappointed. I think the commercial arguments are not very strong. You can find all the information about phase I trials on the Internet if you understand medical terms, are Internet-savvy and speak the right language. I am sure the companies know exactly where to look, because patients seek advice, share knowledge with other patients and have no reason to withhold information."

He points out that a patient-run unofficial Glivec site (www.newcmldrug.com) includes a lively discussion about a new drug for CML being trialled by Bristol-Myers Squibb, BMS-354825/dasatinib. "We pretty well knew about BMS from the day it started in human trials."

But Widler from Roche doubts whether registries would help patients in a phase I setting. "Generally, once you have approval for phase I, the trial starts virtually the next day. By the time a patient finds out through the registry, the trial is already finished."

Roche and IFPMA are discussing the possibility of a separate section of the register, where sponsors could outline the main thrust of a phase I trial and doctors or patients could register an interest in new products.

"If the emphasis is to give access to patients who basically have no hope on the basis of current therapies, then the design of the trial, the 20 fields, the fact that the industry has some reservations because of intellectual property, all become irrelevant. The only thing you need to know is that there is something out there that has a potential to treat my condition, and I would like to be part of it," says Widler.

There are ethical questions about the digital divide and how some patients would get access to trials which others never hear about. But Sim from WHO does not think that registries affect this problem. "There is biased recruitment now and registration does not change that. Patients are being recruited and they are hearing about trials. With delayed disclosure, what would be lost is the sense of transparency and accountability in the short term. You would not be able to search for trials on a website. But patients would still find out about trials and get in."

There are also ethical concerns about patients chasing trials that have little to offer. Widler says patients should understand that when they join a phase 1 trial they are hoping for a miracle. "We are talking more about hope than about a medicine or treatment. We need to be very careful how we deal with this."

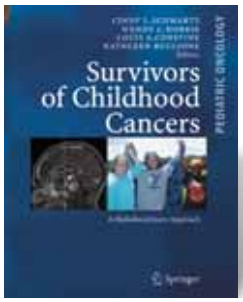
However, Jan insists that many patients can only survive with what are seen as exploratory trials. He believes it is important that patients enrolling on trials find out about the background and rationale. "How can patients give informed consent without listening to their doctor and informing themselves about the trial?"

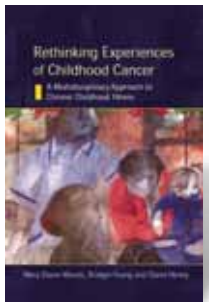
A recent study (NEJM 2005, 352:895–904) showed that the response rate to phase I clinical trials for cancer patients averaged 10.6% with large variations between trials.

It is unlikely that the gap between the hopes of campaigners for open information and the fears of industry and academics about competitive advantage will be bridged before the public debate in Geneva. An era of total openness has not arrived, but a dramatic reduction in the extent of commercial secrecy is under way. How far and fast that will go may depend on who blinks first.

"We pretty well knew about BMS-354825 from the day it started in human trials"

Surviving childhood cancer





➜ Raphaël Brenner

Sociological studies and long-term follow-up of childhood cancers are receiving increased attention. Two new books will enable healthcare providers to better understand the impact of childhood and adolescent cancer therapies.

Why should the effects of treatment carried out on children 30 years ago merit study, when such treatments are out-of-date? The answer, write the authors of *Survivors of Childhood and Adolescent Cancer*, is that one should ascertain the late effects of therapies, regardless of those in use today. Furthermore, since 75% of children with cancer survive today, there is a growing obligation to assess the adverse effects of therapies on their physical, intellectual, psychological and social development. The book aims to update our understanding of the long-term consequences of cancer therapy and addresses issues related to pathophysiology, clinical manifestations, detection, screening and interventions. The editors of this new edition can be commended for clearly presenting a wealth of invaluable material, extracted from thousands of articles, and for covering every facet of survivorship, from medical complications (neuroendocrine, ocular, gastrointestinal, haematopoietic, etc.) to psychological (post-traumatic stress disorder), social, economic and legal (US only) aspects. Consider cardiotoxic anthracyclines for example. While it is true that no congestive heart failure excesses have been noted in patients who were given low doses of doxorubicin, the follow-up period is relatively short. But what will happen in the next 20 years? Will 40-, 50- and 60-year-olds who received treatment decades before show latent damage? Fortunately, since 1990, when this book was first published, both medical and psychological survivorship issues have received increased attention, and follow-up of cancer survivors is now well established. Nevertheless, warn the authors, survivorship is a young science and "we still are on a journey toward the goal of optimising the quality of survival for children with cancer". In *Rethinking Experiences of Childhood Cancer*, Dixon-Woods, Young and Heney (a sociologist, psychologist and paediatric oncologist) highlight the need for further sociological studies of childhood cancer. While the sociology of child health has been well explored, the development of a properly elaborated sociology of childhood illness has been hampered by the dominant developmental approach to childhood, which views childhood as a progression towards adulthood. The 'new' social studies of childhood view children as agentic, meaning that children should be seen as active and giving meaning to their own experiences. The authors depart, however, from some of the other main tenets of these new social studies of childhood. They argue that an interpretative interdisciplinary approach is needed, and that to dismiss psychology in such studies is misguided. Finally, they show that childhood cancer does not affect just children, it affects their parents as well and it is vital to take into account the roles parents play in the process. An informative, lucid, though sometimes recondite book.

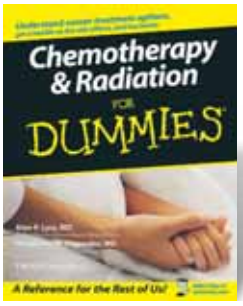
Survivors of Childhood and Adolescent Cancer: a multidisciplinary approach
2nd edition
Edited by Cindy L. Schwartz, Wendy L. Hobbie, Louis S. Constine and Kathleen S. Ruccione
Springer, 372 pp, euro 129.95

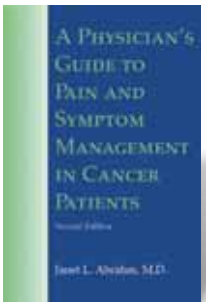
Rethinking Experiences of Childhood Cancer: a multidisciplinary approach to chronic childhood illness
Mary Dixon-Woods, Bridget Young and David Heney
Open University Press, 220 pp, £19.99

Chemotherapy & Radiation for Dummies

Alan P. Lyss, Humberto M. Fagundes and Patricia Corrigan
Wiley, 384 pp, £14.99

The work of a medical oncologist, radiation oncologist and breast cancer survivor, this book, in the well-known 'for dummies' series, offers cancer patients a mine of useful information and answers regarding chemotherapy and radiotherapy. The issue of bone marrow transplants, for instance, is extremely well explained. Avoiding the dry, heavy tone of many patient medical guides, the authors have managed to write an easy-to-read book in lay terms, spiced with humour. With a good glossary, useful definitions and lots of illustrations, it skilfully succeeds in demystifying cancer therapy. The book can be read straight through, or you can just flip through it, choosing the subject you are most interested in. In addition to dealing with the nitty-gritty of chemotherapy and radiation, this compassionate and very practical book deals in detail with the issues facing cancer patients in their daily lives, and fully addresses the need for extra-medical therapeutic aids such as yoga, psychology, massage, spirituality, etc., and the much-neglected issue of post-treatment quality of life. The book lacks a bibliography, but is a welcome addition to cancer patient literature.





A Physician's Guide to Pain and Symptom Management in Cancer Patients

2nd edition
Janet L. Abrahm
The Johns Hopkins University Press,
520 pp, $24.95

"The foundation of our relationships with patients and their families is profoundly affected both by how we first tell them they have cancer and by how we deal with their response to the news," writes Janet Abrahm, director of the Pain and Palliative Care Programs at the Dana-Farber Cancer Institute. Abrahm maintains that the causes of suffering experienced by cancer patients – whether they be physical, psychological, social or spiritual – should be addressed at every stage of the illness and treatment process, from diagnosis, to curative therapy, recurrence and in the final months of a patient's life.
Part I discusses issues such as communication that need to be addressed in order to provide optimal care to cancer patients and their families. Part II offers a detailed review of the technical aspects of symptom assessment and management, covering both the therapeutic protocols for the most common problems, as well as non-pharmacological strategies (alternative medicine, body–mind interventions). An excellent chapter focuses on bereavement and offers examples of how to maintain contact with bereaved families (through regular letters of sympathy, etc.) Both sections include case histories illustrating problems and dilemmas presented by patients and their families. The author reminds us that "both superior communication skills and technical expertise are required if we are to succeed in relieving the distress of cancer patients."
This is an important, intelligent and well-researched book, which includes a bibliography for clinicians and one for patients. It is written with genuine concern for patients and should be particularly useful to clinicians who wish to enhance their relationships with patients and their families.

Traité de Pancréatologie Clinique

Edited by Philippe Lévy,
Philippe Rusziewski and Alain Sauvanet
Flammarion-Médecine-Sciences,
432 pp, euro 85

Pancreatology has greatly expanded in recent years, primarily as a result of advances in medical imaging. This book offers a thorough review of all pancreatic pathologies, devoting the first part to malignant pancreatic tumours, primarily pancreatic adenocarcinoma. The authors stress the importance of experience

in the overall management of adenocarcinoma, noting a post-operative mortality of 0%–5% among highly specialised teams which carry out a high volume of pancreatic surgery, against 10%–12% in non-specialist centres. Chemotherapy (gemcitabine) has proven to be important in advanced pancreatic adenocarcinoma. Surgeons and oncologists will find in this book up-to-date information on all the rare pancreatic tumours (endocrine tumours, leiomyosarcoma, cystadenocarcinoma, etc.). As a result of medical imaging, physicians now know much more about intraductal papillary-mucinous tumours, which are not as rare as once believed. Advances in knowledge notwithstanding, the overall survival rate for pancreatic cancer patients remains terribly low, registering the lowest improvement of all types of cancers in the last decades.

Textbook of Malignant Hematology
2nd edition
Edited by Laurent Degos, David C. Linch and Bob Löwenberg
Taylor & Francis, 892 pp, £185 (hardback)

Hematology in Clinical Practice
4th edition
Robert S. Hillman, Kenneth A. Ault and Henry M. Rinder
McGraw-Hill, 480 pp, £39.99

Hématologie Clinique et Biologique
2nd edition
Edited by Gérard Sébahoun
Arnette, 590 pp, euro 75.00

IT is not very often that a textbook offers pleasurable reading. The *Textbook of Malignant Hematology,* by Degos et al, belongs to this rare category of book. The authors, who are mainly European, focus on recent insights into the pathophysiology of haematological malignancies and on the scientific principles underlying current therapies. In 47 chapters, their book paints a complete picture of malignant haematology and includes sections on normal and malignant haematopoiesis. The chapter on immunosuppression (Epstein-Barr virus and other herpes viruses in haematological malignancies) perfectly illustrates how the molecular mechanisms determine the clinical expression.

Comparing it with the 1st edition, it is clear that most chapters have been considerably revised, and many new chapters have been added, such as those covering stem cell plasticity, DNA repair, senescence and telomeres, angiogenesis and tumour development, microarray analysis (very well explained) and expression profiling. Specific chapters are also devoted to paediatric haemopathies, and more emphasis and space (three chapters) have been accorded to the late effects of therapy. As to be expected in such a heavyweight book, there is no dearth of bibliographical references (almost 500 just for the excellent chapter on allogenic stem cell transplantation), but given the book's overall quality and price, one would have wished for a less dense layout. It is almost indecent not to have more four-colour printing than the few colour plates at the beginning of the book. This would certainly have made it easier to decipher, for example, the illustration of T-cell development in the thymus. That said, this immensely comprehensive book will be an invaluable aid to haematologic malignancy specialists and oncologists as well as to students and trainee physicians alike.

Less ambitious and less detailed than Degos, Hillman specifically caters to clinicians. It covers haematology in general, devoting part II to malignancies (excluding child malignancies). The authors have opted for a thoughtful approach to the presentation of the core knowledge and make good use of tables, algorithms, practical figures and bold print to accompany a clearly written text. The use of two-colour printing throughout the book makes it a user-friendly guide for diagnosis and treatment.

Sébahoun's book covers more or less the same scope and content as Hillman, but lacks colour, has no bibliography and offers few figures or illustrations. As such, it does not facilitate the reader's task. It lacks, for example, a vital classification table for acute myeloid leukaemias, which one finds in both Degos and Hillman. Should books for students and trainee doctors look so sad and forbidding? Just as with Heidegger, it seems that publishers and editors sometimes forget that before 'being' comes 'well-being.'