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Hein van Poppel

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Tackling the adherence crisis

Kathy Redmond ■ EDITOR

Two recent reports are flagging up a problem of near crisis proportions that is leading to unnecessary disease progression, reduced quality of life or even death, and costs an estimated $150–$300 billion annually in the US alone. The US National Council on Patient Information and Education is talking in terms of "America's other drug problem"; the WHO is calling it "a worldwide problem of striking magnitude". Both refer to a growing crisis of 'non-adherence' – patients not sticking to their prescriptions – which has so far been overlooked as a serious public health issue, despite the high human and financial cost.

It has been estimated that on average only about 50% of patients take their medicines as prescribed, with rates varying across diseases, drug regimens and age groups. Older people, adolescents and those with chronic diseases requiring long-term treatment are thought most likely to stray from their prescriptions.

The problem is not confined to patients with less severe illnesses. In cancer, non-adherence rates ranging from 20% to 100% have been reported, including for adjuvant endocrine therapy, supportive care and treatment with oral targeted therapies. The situation is likely to get worse as more oral cancer drugs come on the market, particularly as many of them have no defined treatment timeframe.

Interestingly, the pharmaceutical industry, concerned that widespread non-adherence to prescriptions could impact on profits, has itself flagged this up as a major issue. Consultants *PriceWaterhouseCoopers* recently published a report encouraging pharmaceutical companies to invest in developing monitoring and mnemonic devices to help patients stick to the instructions on the side of the box.

The reasons for non-adherence cited by the National Council on Patient Information and Education report, *Enhancing prescription medicine adherence: a national action plan* (http://www.talkaboutrx.org), include lack of awareness among clinicians about basic adherence management principles, poor communication between patients and clinicians, operational aspects of pharmacy and medical practice, and professional barriers.

The report sets out 10 recommendations, which include prioritising medicines adherence as a serious public health problem, providing comprehensive professional training in adherence management, sharing best practice in effective management approaches and increased funding for adherence-related research to help demonstrate what works.

Frontline health professionals will be key to making this action plan work. We are the ones who can help patients understand their disease and how the medication, taken correctly, can help, by giving them tailored information and taking time to talk everything through. We are the ones who can manage side-effects and can routinely check with patients how and when they take their medication. We are the ones who, when a patient fails to respond to a therapy, can pause to consider whether the problem may be adherence rather than lack of efficacy.

We need to do it – and do it now.

Hein Van Poppel:

Urological cancer is what we do

➜ Marc Beishon

Hein Van Poppel, director of the European School of Urology, is driving forward the training and accreditation of Europe's urological oncologists. He wants to see an end to untrained urologists dishing out cancer medicines – but he is no more keen on medical oncologists who treat kidneys, prostates and bladders without any specialist training in these organs.

People working in cancer often look back over the last few decades and see an era of enormous progress in understanding and treating the many oncological diseases. But there are other medical fields that have seen equally remarkable progress, none more so than urology, which in just 25 years has developed from a minor surgical specialty into a major, complex surgical and medical discipline with a number of 'super-specialties', including neurological, female, paediatric and reconstructive urology, and of course oncological urology.

And it is oncological urology that is very much at the centre of the debate on the delivery of cancer treatment in Europe, in particular the arguments between specialists who practice medical oncology and the movement to bring more specialties into a common oncology 'society'. For Hein Van Poppel, chair of the department of urology at the Catholic University Hospital in Leuven, Belgium, and a leading light in all manner of urology and oncology organisations, the issue is straightforward.

"Urologists are different to other specialists such as gastro-enterologists and abdominal surgeons. We do everything for the patient, from diagnosis through to surgery, medical treatment and end-of-life care. We have delivered treatments such as hormonal drugs for years and there is no reason not to administer cytotoxic and newer targeted therapies, as we know the urological malignancies of our patients much better than many medical oncologists. How can they be a specialist in the treatment of all different organ cancers just because they have tools such as cytotoxic therapies that are difficult to manage? The tool does not allow you to master the organ – that is an error in the mind of many medical oncologists. It is more important to know the patient than to know the drug."

The proviso – and it is a hugely important one – is that such care must be delivered by trained and preferably accredited oncological urologists, ideally in a multidisciplinary setting. In academic centres such as at Leuven, that expertise is a given, and as Van Poppel adds, "In fact, it is not important who delivers the therapy indicated in multidisciplinary discussions. It could be the urologist or medical or radiation oncologist, as long as they can deliver a drug with the same pertinence and safety."

Belgium, says Van Poppel, is now taking a lead in Europe in developing an oncological accreditation for urologists that allows them, just like medical oncologists, to prescribe and administer medical cancer treatments. He points also to new initiatives that are

TIM DIRVEN/PANOS PHOTOGRAPHY

State-of-the-art. Van Poppel with the latest addition to his oncology department – an impressive piece of robotic technology that surgeons can use to improve precision, stability and dexterity

building bridges between the oncology specialties. In Barcelona this year, the European School of Urology held its second masterclass on medical treatment of urological malignancies, sponsored by the European Association of Urology (EAU). From next year this masterclass will also be open to medical oncologists and other cancer specialists. Then in November, also in Barcelona, the first European Multidisciplinary Meeting on Urological Cancers will be held, with "for the first time in history", the EAU, ESMO (European Society for Medical Oncology) and ESTRO (European Society for Therapeutic Radiology and Oncology) joining urological forces to focus, in this event, on prostate and kidney cancers.

Van Poppel is heavily involved in such training and education. He is director of the European School of Urology, the education office of the EAU – "This, together with membership of the ESMO faculty, is the most important of all my international roles." Flagship masterclass and resident training programmes for all urologists in Europe, in addition to the new oncology events and the growing influence of the EAU's annual congress, all contribute to making urology one of the most powerful and high-profile disciplines in Europe – closely rivalling cardiology, he reckons.

"The multidisciplinary meeting on urological cancers is especially important politically for European urology. I believe we can deliver education that is at least as good as the one offered by other societies in the US. I have 150 teachers in the European School of Urology faculty and 40% are oncology experts."

On the cancer side he is also, naturally, active in the European Society of Surgical Oncology (ESSO), and the European Organisation for the Research and

"It is more important to know the patient than the drug"

Treatment of Cancer (EORTC). During his career at Leuven he has developed local expertise in radical prostatectomy and partial nephrectomy and bladder replacement, while also leading landmark international research on both techniques.

The rigour and breadth of Van Poppel's oncological experience is impressive, and he is more than qualified to turn the call for organ-based specialism onto medical oncologists themselves. "Medical oncologists have an almost exclusively pharmacological approach to cancer, based on its own physiology. But cancer is a disease of organs and is much more than physiology. It is a complex disease involving many aspects of the human being including symptoms and side-effects. Urological oncologists are organ driven, and able to see the complexity of the tumour and apply oncologic surgery and radiotherapy, and use different drugs. Many radiation oncologists have for some years dedicated themselves to certain organs and we have uro-radiation oncologists who belong specifically to our care programme. All I ask is that medical oncologists know as much about urological diseases as we do – and that really means being dedicated to certain organs as we are."

A Belgian from the Flemish side of the country, Van Poppel trained for three years at the French-speaking Namur University before completing medical school at Leuven, gravitating to surgery in his final year. "I believed I could do more for patients with surgery, and was set for a career in general work at a community hospital until I was asked if I wanted an academic appointment at Leuven's urology department. The dean of the faculty of medicine sent me abroad for two years and, although I was working on a thesis on neurogenic bladder, I met, among others, oncology specialists Fritz Schroeder in Rotterdam and Rudolf Hohenfellner in Mainz. They convinced me their field held the most interest." He also gained much experience as a pupil of the famous Barcelona-based surgeon José-Maria Gil-Vernet – still a close contact.

He returned to Leuven, finished his thesis, but moved on to specialise in oncological urology,

Committed to education. Van Poppel with faculty member Joaquim Bellmunt, at the second ESU masterclass on medical oncology for urologists, held in Barcelona earlier this year

"All I ask is that medical oncologists know as much about urological cancers as we do"

gradually phasing out work in other subspecialties over the years. "Urology then really was the poor relation in surgery at Leuven and elsewhere – we were just doing foreskins, transurethral operations and so on. I totally disagreed that after doing a couple of years of general surgery and some endoscopy you became a urologist, with the 'big surgery' such as nephrectomies handed to other surgeons. We felt pushed in a corner – and we pushed back, and have been ever since."

Following the lead of surgeons such as Schroeder, who came back from the US to introduce radical prostatectomy, the technique that should, in the right hands, spare functions such as continence and potency for certain grades of tumour, Van Poppel and colleagues transformed their department to one that handles all major urological surgery and treatment. In 2002 he became department head, adopting a policy of giving colleagues their head to develop other key specialties, while he focused on oncology.

"This has been tremendously successful – I've seen other units where the chief tries to keep on top of everything and it just doesn't work. We need specialists who can develop their own care, teaching and research programmes. The surgeon who is very good at endoscopic transurethral resections of the prostate is probably not the best to do extensive lymph node dissections after chemotherapy – it's a different type of surgery."

The development of specialisms across the five main pillars of urology, as he calls them – paediatric, functional, reconstructive, endourology and oncology – did need some careful guidance on his part, and a particular aim was to bring the unit to international attention. That has been achieved with a focus on state-of-the-art surgery and leading and participating in key research topics, such as radical prostatectomy on the oncology side.

Working conditions have also improved greatly. The urology unit moved from an old hospital in central Leuven to join a huge modern site called Gasthuisberg on the edge of the city (despite its small size, the city of Leuven has long been competing with Brussels as the Belgian capital). This university hospital has some 1,800 beds and is a major centre in the Flanders region, also attracting patients from abroad. "We now have our own outpatient department and clinic for small operations across two floors of the hospital. We were able to convince the management that we were growing so fast we needed dedicated facilities."

There is a large volume of urological work. "Each morning we discuss all hospitalised patients – there are more than 40 – and I run an outpatient clinic once a week for 30 people with often second/third opinion oncological problems. On days scheduled for oncology surgery we do two to four major cases – say four radical prostatectomies or two bladders. People have said we are crazy to do so many in one day, but if we don't, we end up with a waiting list that's too long."

Leuven is a referral centre for difficult cases such as vena cava thrombus and salvage surgery after chemo- or radiotherapy, and also carries out operations that are not widely available in some other countries. "Take radical prostatectomy for locally advanced cancer – many urologists don't do this, sticking to guidelines that in some countries recommend hormonal and radiation treatment. But when patients are clever, they find out about the success rates of surgery and ask for radical prostatectomy – and when they can't get it they come here." Men from Scandinavia are among those arriving at Leuven, he says.

"For patients with locally confined prostate cancer, I prefer to use the term 'total prostatectomy', as the word 'radical' makes men rather afraid," he says. "It's a marginal resection that preserves the neurovascular bundles and sphincter. Surgeons who tell their early prostate cancer patients they will lose their potency because they can't do nerve sparing surgery need retraining."

Van Poppel is certainly an authority on radical prostatectomy, having performed more than 1,800 operations himself. He has also introduced techniques such as robot-assisted laparoscopy, in place at Leuven for a few months now. But he is clear that quantity does not necessarily mean quality. In an

"Surgeons who tell early prostate cancer patients they can't do nerve sparing surgery need retraining"

evaluation of surgeons in EORTC's genito-urinary group, he found that meeting higher quality parameters did not relate always to a higher caseload.

"A very high volume may not be better, because the surgeon may not find the work challenging enough or because he continues to make the same errors during every surgery. I believe oncological and urological outcomes are the only factors that should allow urologists to continue with this type of surgery. Analysing just a couple of parameters in 10 early prostate cancer operations can assess their surgical skill."

Van Poppel set this out in a paper in the *European Journal of Cancer* in 2001, where duration of surgery, transfusion need, post-operative PSA (prostate specific antigen), status of the surgical margins and incontinence were assessed. "A certain volume of procedures is probably needed to gain and keep experience, and maybe 25 to 40 procedures a year per surgeon is optimal." This was also concluded in a recent presentation at the American Urological Association by a multi-centre European–Canadian study. But it may be a tall order to raise the bar across Europe for this operation, given that minimum case loads in some countries are as low as five.

Other research he highlights with the EORTC is a study he coordinated with Michel Bolla from Grenoble that showed the benefits of post-operative radiotherapy for high-risk prostate cancer patients. But perhaps his landmark work is performing some of the first series of partial nephrectomies in Europe (where only part of the kidney is removed) and an EORTC trial that he designed and coordinated of a prospective comparison of partial versus radical nephrectomy in low-grade renal carcinoma. "It has become obvious that nephron-sparing surgery decreases the possible occurrence of renal failure and the need for dialysis, and this phase III study aimed to look at complication rates and oncological outcomes." It involved more than 40 centres and was also opened to intergroup study in North America, although the latter could contribute only few patients, notes Van Poppel.

"It was closed prematurely because everyone was doing partials without waiting for the results. We are now doing the analysis and will publish in early 2008."

Leuven is active in plenty of other research. "Denditric cell vaccination treatments and microarray work for kidney cancer, photodynamic diagnosis with hypericin [an extract from St John's wort] for superficial bladder cancer, choline PET-scan for sentinel lymph node investigation in prostate cancer and, even more importantly, chemoprevention trials for bladder and prostate cancers are all ongoing," he notes. New minimally invasive treatment strategies with percutaneous radiofrequency ablation for kidney tumours and high-intensity focused ultrasound for prostate cancer are also being explored in prospective multicentre studies. Overall, he and colleagues have a prodigious oncology research volume.

While much of Van Poppel's research revolves around surgery, he is just as well up on the many new drug treatments, and was course director, with close friend Ziya Kirkali from Turkey, of the second Barcelona masterclass on medical oncology for urologists. This course had four modules – hormone and intervesical therapy, chemoprevention and immunotherapy, targeted therapy and cytotoxic chemotherapy – and there are many new approaches now in phase II and III studies. There was a European Board of Urology examination at the end, leading to a certificate that will be useful in the accreditation of urological oncologists, says Van Poppel. "The difficulty of the exam is high and, of the urologists taking it, younger ones did

"Maybe 25 to 40 procedures a year are needed per surgeon to gain and keep experience"

Off duty. Van Poppel enjoys a beer with his wife Conny and their three girls Ineke, Loesje and Ellen

better than older colleagues. By the way – Belgium was the best represented country on the course."

Although practices differ around Europe, there are common patterns in who is delivering certain drug therapies. "Medical oncologists are only involved in part of the treatments for the malignancies we see. In most countries this is interferon for kidney cancer, and cytotoxic chemotherapy for bladder, testicular and penile cancer. Hormonal therapies for prostate cancer are given by urologists – we have long been approached by the drug companies to deliver these – and we can now deliver new treatments for kidney cancer."

The key is of course multidisciplinary consultation, with all participants increasingly dedicated to urology, which Van Poppel recognises will be very difficult in smaller hospitals. But clearly the path he is set on is for urologists to involve themselves more in all aspects of care, in the absence of commitment from medical oncologists (who, to be fair, he says are not present in enough numbers in most European countries). "But every patient with an oncological problem should have the right to have his case extensively discussed by all the specialists involved in the diagnosis, the staging and the treatment of his disease."

What must be policed, however, are urologists in outlying clinics who think they can prescribe drugs, say for metastatic prostate cancer, while practising as an everyday all-round urologist. Only two years of supplementary oncology training for newcomers, and rigorous accreditation at the likes of the ESU's masterclasses, and by country agencies, will do, he says.

Equally, medical oncologists must recognise, he adds, the danger in prescribing treatments for say metastatic renal carcinoma without discussing the case with the urologist and other surgeons, as surgical intervention may offer a better chance, say for a pulmonary metastasis. "Medical oncologists who attend our masterclasses will learn about this and other topics, such as knowing you have to stop drug therapy at a certain stage in superficial bladder cancers and perform a cystectomy," he says.

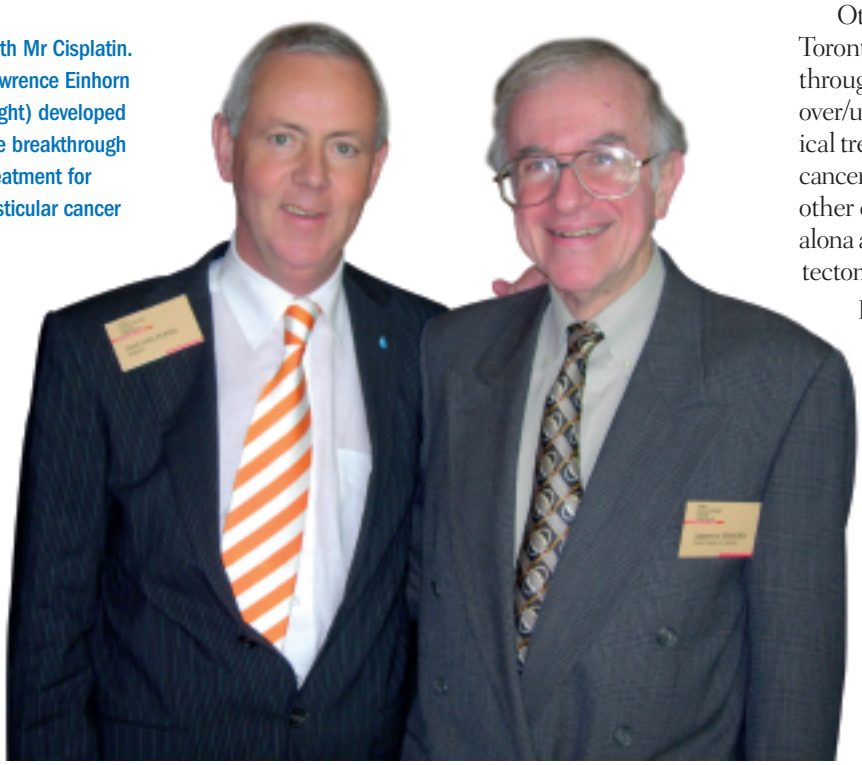
It all boils down to who knows the treatments – and the patients – the best, and if he could, Van Poppel would also reverse the trend for specialist palliative care units and let patients remain in the hands of their primary physician.

"If you find a small cancer and carry on surveillance, noting a rising PSA, how long do you wait?"

When it comes to his most broad interest, Van Poppel's focus is firmly on prostate cancer and the entire life cycle of the disease, including its possible prevention. "Most of the research so far on green tea, lycopene, vitamin E and so on has been badly done, but it is important we find out if there is something we can offer men, especially those with a family history of prostate cancer. Chinese men have as much PIN [prostate intraepithelial neoplasia, or carcinoma in situ] as men in the West, but ten times less invasive cancer. The only way to investigate is through randomised trials in high-grade PIN patients. We have done this with soy, vitamin E and selenium, and are now doing it with lycopene, and we will move on to other agents."

Treatment guidelines for the various cancer stages and ages are also a big concern, especially as overtreatment is a common problem – and conversely, adopting an 'active surveillance' approach may mean a window for optimal treatment may be missed. A critical age group is younger men aged 50–65 – as Van Poppel says, if you find a small cancer in a 50 year old and carry on with surveillance, noting rising PSA levels, how long do you wait?

"With a Gleason score of 6 [where cancer cells are moderately differentiated], you can have a radical prostatectomy, where the only drawback of the surgery should be loss of fertility. But if you wait, many men will suffer years of anxiety, and you risk a more extensive operation with less chance of a cure." He notes the difficulty of recruiting younger men into active surveillance trials, where the end point is time to metastasis, and which also involve biopsies and attendant risks. "I don't think this should be encouraged. With a Gleason score of 6 or 7 and a PSA of less than 2.5 you still can't cure all cancers with radical prostatectomy. You and the patient are taking a risk by waiting."



With Mr Cisplatin. Lawrence Einhorn (right) developed the breakthrough treatment for testicular cancer

Other urologists, in particular Laurence Klotz in Toronto, are promoting delayed radical intervention through active surveillance as the best balance in the over/undertreatment debate. Men who have had radical treatment can also suffer as much anxiety (about cancer recurrence) as those on watchful waiting. In the other camp are other top urologists such as Bill Catalona and Van Poppel, favouring earlier radical prostatectomy. It is currently the only treatment for localised prostate cancer that has shown a cancer-specific survival benefit when compared to conservative management in a prospective, randomised Scandinavian trial. "Early surgery will allow the patient to recover urinary and sexual function with a very high likelihood of definitive cancer cure," he says.

It is only men aged 65 and over who are offered curative radiation therapy in the Flanders region covered by Leuven, except in exceptional circumstances. "If you're below 65 and approach our radiation oncologists for treatment, such as external beam or interstitial radiotherapy, they will refer you to me," he says. "It's not just that there is less chance of a

cure, but salvage surgery can be very difficult. But above 65 the impact of surgery on quality of life is greater and survival is comparable." Above 75, hormonal therapy is sometimes more than enough to allow the patient to reach his normal life expectancy without ever suffering any cancer symptom.

What does concern Van Poppel is that the best management is only possible in centres where the widest choice of treatments is available. Leuven has open and laparoscopic (now robot-assisted) surgery, radiotherapy (including brachytherapy), and high-intensity focused ultrasound and IGRT (image-guided, intensity-modulated radiotherapy). "The only one we don't have is cryotherapy (freezing therapy). Patients need an honest opinion on what is best for them – but there are specialists whose salaries are linked to certain treatments and they will convince the patient that their modality is best."

Like many *Cancer World* interviewees, Van Poppel is particularly critical of overtreatment, mentioning that radical treatment is being offered to men with the carcinoma in situ condition (PIN), who are genuine candidates for watchful waiting, since they have no invasive carcinoma. And brachytherapy is one curative treatment option where patients and doctors may be jumping on fashion. "Propaganda on the Internet is certainly to blame, and I feel it is often given to men who probably don't need treatment at all." It's also a treatment that, like radical prostatectomy, can be performed badly, he adds, and the decision is critical given that you only have one chance at the best treatment.

He says the best promoters of better treatment standards are undoubtedly patient groups, with Europa Uomo, the European Prostate Cancer Coalition, very much to the fore. Van Poppel is the advocacy organisation's scientific chairman, and says he is impressed by how much work has already been done in developing links with national groups since it was founded in 2002. "I give the board an update on prostate cancer at its general assembly, and it is a difficult talk, as they know more about it than some doctors," he says (slides of his latest talk are on Europa Uomo's website, which can be reached at www.cancerworld.org).

A priority is PSA testing, he says. "PSA testing first at age 40 and then at 45 and 50 – the age when men start to develop cancer – will help to show who is at risk of developing dangerous disease and who will need more strict follow-up. Patient groups will be much more effective at lobbying governments for more affordable PSA tests than doctors." Access to second opinions and countering inappropriate treatment are also priorities for patient coalitions such as Europa Uomo, he feels. "At Leuven, we held a recent event in which 300 patients discussed their experiences of living after radical prostatectomy," he adds.

Van Poppel plans to continue his clinical and teaching roles at Leuven, although he is envious of urologists who have their own research labs. "I'd like to run one like Fritz Schroeder's in Rotterdam and Frans Debruyne's in Nijmegen. I'm working on it. Prostate cancer research would be my priority."

Outside of Leuven, his aims are to continue to raise educational standards for urologists in Europe and further afield. "All European urologists should pass the European Board of Urology exams – it must be a minimum requirement" – and he is in favour of legal measures to compel continuing education.

Home life for Van Poppel is calmer now that his three daughters are grown up, although he and his wife Conny still organise family holidays – the latest to Barcelona, which just happened to be where ECCO, the congress of the European CanCer Organisation was taking place. On a personal note he talks of a recent case of cancer in his close family – despite working with cancer patients for many years this has really brought home to him just how important it is, as a doctor, to relate to people. When he has spare time he likes to play golf – just don't ask about his handicap.

The Leuven school of urology has a logo made up of a drawing of the male and female urological and the male genital organs by Philip Verheyen, a 17th century Flemish anatomist and surgeon at Leuven. Verheyen's mission – to understand underlying physiology before embarking on disease treatment – could hardly hold more true for Van Poppel and colleagues today.

"The best approach is only possible in centres where the widest choice of treatments is available"

Dying for a lack of compassion?

Anna Wagstaff

For dying cancer patients who have run out of therapeutic options, getting hold of drugs that are still in trials can offer them a last throw of the dice. Yet many find the system for getting early access to drugs, for so-called 'compassionate use', is beset by obstacles and delays. They want a greater sense of urgency… and a greater say.

In June this year, the Life Raft Group – an advocacy organisation for patients with GIST – celebrated its 5th anniversary by looking back on its achievements and taking stock of how far knowledge about this relatively rare cancer and its treatment has progressed.

An anniversary newsletter carried articles on the 10 research groups that Life Raft is funding and on interesting findings from their own surveillance programme, in which 820 Life Raft members to date have agreed to submit details of their diagnosis, treatments and responses. Another piece offered an overview of current knowledge of the various mutations in GIST, looking at how these affect resistance to different therapies and discussing the value of trialling combination regimens.

This patient group is putting enormous work into getting to grips with the science behind their disease and co-operating with and contributing to the research effort that is helping keep them alive. However, in an upbeat anniversary publication, one article stands out because of its tone of exasperation and sadness. Written by executive director Norman Scherzer, it talks about the Life Raft members who are dying without getting a chance to try the new therapies that everyone is talking about, even though they are available for clinical trials.

He picks out for special mention two patients who had stopped responding to imatinib (Glivec). One was seeking urgent access to sunitinib (now marketed as Sutent); the other had already tried and failed on sunitinib and wanted to try dasatinib (now marketed as Sprycel). Both drugs have since been approved for patients who have failed on Glivec (Sutent for GIST, Sprycel for chronic myeloid leukaemia), but even then, before approval, some information was known about the drugs, and the patient community had been following them closely since before they entered human trials. Reports received from researchers and via the Life Raft network looked encouraging.

One of these patients had voluntarily come off a trial for sunitinib, on the mistaken belief that the drug was causing unacceptable side-effects. When he found out he had been on placebo, and the symptoms were due to the progression of his disease, he applied to rejoin the trial, but was refused. In the case of the second patient, the only trial within conceivable reach had completed enrolment. With the help of the Life Raft Group, both patients tried to get hold of the drug outside of the trial, on a so-called 'compassionate use' basis. But a combination of obstacles in getting hold of the drug and agreement for it to be administered outside the trials proved insurmountable.

"What could justify not getting a drug to a dying patient in a reasonable period of time, say a few hours or at most a few days?" asks Scherzer, who has fought endless battles with various parties to secure access to patients like these. "There is a feeling of helplessness as patients and caregivers try to navigate this institutional landscape to stay alive. It is easy to believe that this system was just not designed to meet the urgent needs of dying cancer patients."

This is true. The system governing access to drugs is designed primarily to ensure that when a new drug enters the market there is strong evidence available on its efficacy and safety, so that doctors

and patients can make informed choices. If investigative drugs are widely available outside clinical trials, patients may have less incentive to enrol in a trial, which could make it harder to gather that evidence. The system is also designed to protect patients from exploitation by those offering false hope or even potentially harmful therapies. Dying cancer patients are particularly vulnerable, as has most recently been demonstrated by the scramble to get access to DCA (dichloroacetic acid), an acid that has shown promising anti-cancer activity in animals, but is available on the market only in forms not suitable for human use (see Do-it-yourself Chemotherapy Access, p 38).

Compassionate use

Within this system, the urgent needs of dying cancer patients are recognised by provisions covering 'compassionate use' – any authorised use, outside of clinical trials, of an investigative drug (i.e. under study but not yet approved). Within the EU, where cancer drug approval is centralised in the hands of the European Medicines Agency (EMEA), Article 83 (1) of Regulation (EC) No. 726/2004 gives Member States the right to make certain categories of drugs available for compassionate use. How they do this – if at all – is up to them.

Many Member States have provisions for expanded access programmes (EAPs). These cover groups of patients with a specified indication, and tend to follow the same protocol as the relevant clinical trial. Their primary purpose is to widen the group of patients who can get access to the drug. Not all companies seek to set up EAPs, and those that do, will only do it for some of their drugs. Programmes tend to be set up once a phase III trial has recruited its full complement of patients, or in countries where no clinical trial is running or, possibly, for patients who are ineligible to join the trial. Such programmes can be used to gather additional information about the drug.

Pressure to set up expanded access schemes is particularly great where a drug is for patients who have few other therapeutic options – and, of course, where it has shown great efficacy in trials. Imatinib was a classic case, given to more than 7,000 patients through an expanded access scheme following dramatic results in phase II trials.

Even though not all EU countries have provisions for running EAPs, it should still be possible to apply for access to an investigational drug for compassionate use on a 'named-patient' basis. This usually requires a patient's physician to contact the company with a request that they supply the drug to their named patient. If the company agrees – and it is a big if – the physician can then apply to their national regulatory body for the go-ahead. They often also need permission from an ethics committee or their local health board before

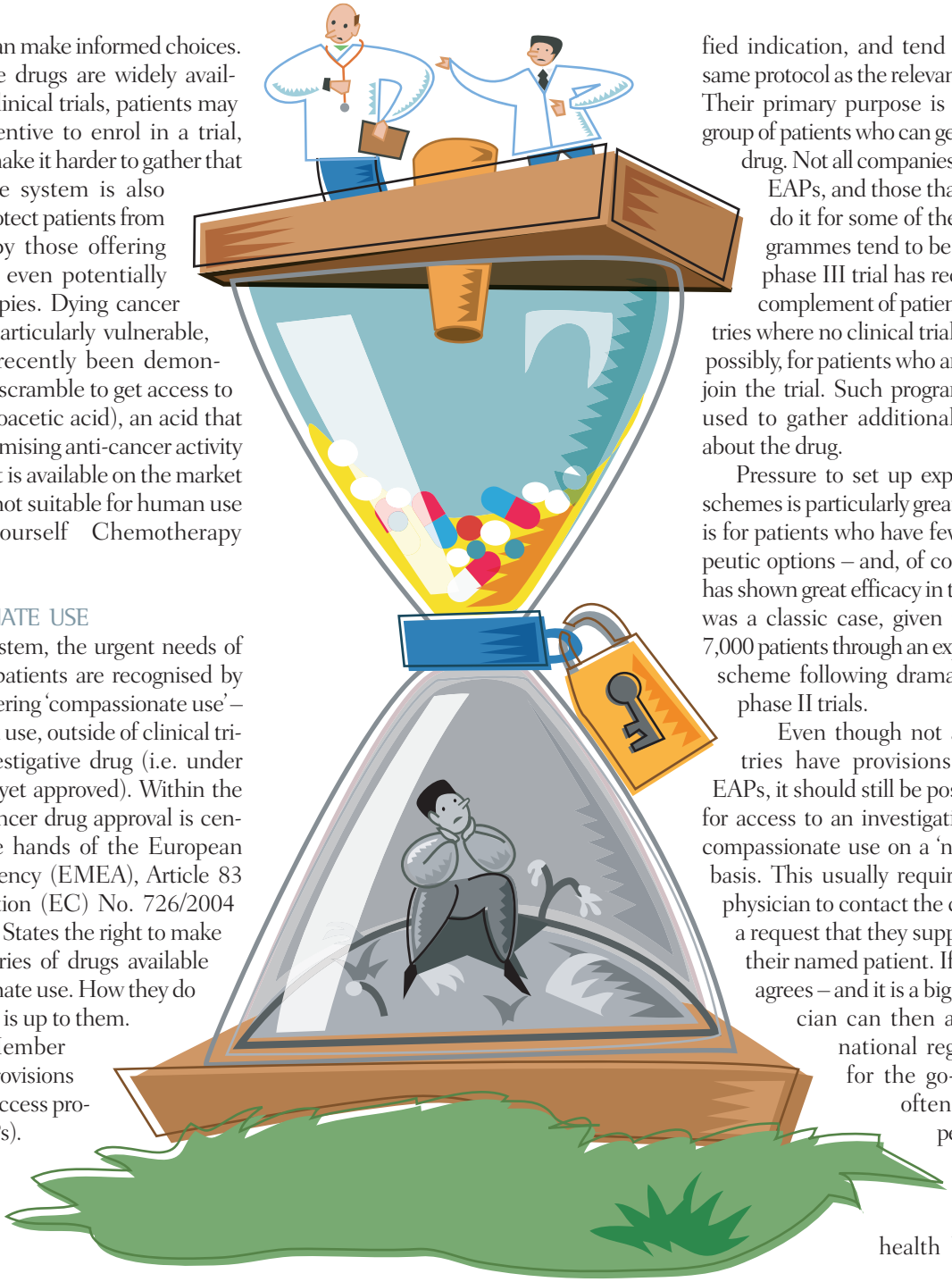


ILLUSTRATION: FRED VAN DEELEN

"There is a feeling of helplessness as patients try to navigate this institutional landscape to stay alive"

they are allowed to administer a drug whose safety and efficacy has not been proven. In most countries, patients can also import unapproved drugs for their own use so long as the drug has been approved in some other country.

Differences between the systems operating across the EU affect the likelihood of an expanded access programme being set up or a given patient getting access on a named-patient basis. In some countries, all drugs supplied for compassionate use have to be paid for by the manufacturer. In others the company may make a charge to cover administrative costs, and in some cases the charge can include cost of production, and even a small element of research and development costs.

In some countries, getting agreement for compassionate use can be very complex and time-consuming, involving bundles of paperwork and discussion at various levels. Others try to keep it simple.

Compassionate use

Compassionate use schemes are a way to give patients access to investigational drugs before they have been given marketing approval. They take two basic forms:
Expanded access programmes (EAPs), which are open to groups of patients providing they meet specific requirements regarding the type and stage of disease
Named-patient programmes, where access is negotiated on a patient by patient basis
In most countries it is also possible to import a product approved in another country, e.g. the US, for personal use
The rules covering compassionate use vary across Europe:

France allows:
- Temporary named use (ATU) – for an individual patient
- Cohort ATU for a group of patients that are treated according to a protocol (expanded access programme)

Germany allows:
- Named-patient sales of products that are approved in another country
- Named-patient programme

Italy allows:
- Named-patient programme for products approved in another country or that have completed phase II trials
- Importation of a product approved in another country for personal use

The UK allows:
- Open-label clinical trials (in which the doctor and patient knows what treatment is being given)
- Importation of product approved in another country for personal use
- Supply of drug on a named-patient basis

Source: A guide to cancer drug development and regulation, AstraZeneca 2006
www.cancerline.com/gUserFiles/Regulatory_Guide_Contents.pdf

Obstacles

Patients face three main obstacles in their quest to "navigate through this institutional landscape". First they have to find out what drugs are being trialled – or are about to enter trials – that might be relevant to their condition.

There is no legal obligation on companies to make this information public, and even when they do, the information can be hard to find, as Europe has no equivalent to the publicly accessible American clinical trials registry www.clinicaltrials.gov.

The WHO is trying to establish a single clinical trials registry platform (see A Trial of Strength, *Cancer World* 11, Jan–Feb 2006), but the industry is resisting demands that they register phase I and II trials quickly enough and with sufficient detail to be of use to patients in urgent need.

In the absence of such a formal system of disclosure, some patient advocacy groups have become adept at picking up this sort of information – for instance by attending the professional conferences, and building relations with researchers from the clinical side and from the industry. Once in the hands of a motivated patient, the information spreads like wildfire via the web – but only to patients who know where to look.

The second obstacle is regulators, ethics committees or hospital boards who don't want to OK the use of a drug when they feel they have too little evidence to evaluate whether it is more likely to help or harm the patient. This is an attitude that has baffled and infuriated dying cancer patients in equal measure. Today's drugs, they argue, are designed to work on specific targets in a specific way, and a great deal is known about every compound long before it reaches human trials. If there is scientific rationale for believing that a drug could conceivably be of benefit, and if that drug is perceived to be safe enough for a

phase I or phase II trial, then patients who have run out of other options and are running out of time, should be given the chance to try it. As one of the patients who campaigned for early access to Glivec put it: "Novartis talks about the safety angle, but long-term side-effects mean nothing to me. If I don't have treatment the only long-term effect for me is death"

The third major obstacle is getting agreement from the manufacturer to supply it. The company's priority is to get their drug through clinical trials and onto the market as quickly and efficiently as they can, and they may fear that patients won't join the trial if they can access the product another way. Companies may also be reluctant to hand out compounds that have not been well evaluated, for use outside the closely monitored and controlled setting of a clinical trial. Even if patients sign a waiver, confidence in the drug might be undermined before it has the chance to prove itself, if its first widespread use is in the sickest patients who are likely to have the most severe co-morbidities and may be the least likely to respond.

The biggest problem for companies lies in the cost and logistics of manufacturing a drug for widespread compassionate use. Early clinical trials need enough drugs for only a few hundred patients, which can usually be produced with basic laboratory facilities. Once thousands of patients are involved, however, major investment in production capacity may be required – something companies are understandably reluctant to do before they are certain their drug will get marketing approval.

In a book about the development of

MARTI'S STORY

Marti Nelson discovered she had breast cancer at the age of 33. It was an aggressive cancer that was given the full treatment: mastectomy, chemotherapy and radiation. Seven years later the cancer had spread to her bones, liver and lung, but by that time a new drug was in trials that Nelson – herself a physician – believed could help her. This was 1994, the new drug was the HER2-neu monoclonal antibody that would eventually become Herceptin (trastuzumab) and it was being developed by Genentech, who were based nearby, in San Francisco. Nelson asked to be allowed to try the drug. Genentech refused, and Nelson died at the end of that year.

Nelson had long been active as a breast cancer advocate, but the big patient voice in San Franciso at the time came from the AIDS community, who were beginning to make progress in their own battle to get companies to give dying patients early access to drugs in development. Why couldn't Genentech do the same for a breast cancer patient? is a question Nelson had asked. The AIDS activists rallied to support. The following year, when another breast cancer patient advocate, Barbara Moulton, called on Genentech for access to the drug, AIDS and breast cancer patients joined forces and organised lively protests outside the company's headquarters.

Genentech argued that if they gave the drug at that stage in development, they would have to track the patients' progress, which would be time-consuming and expensive. They also talked about the costs of production. "We're… talking about a drug made through biotechnology, genetic engineering, which is difficult to make and expensive," a spokeswoman said.

Moulton, like Nelson, died before being given the chance to try the HER2-neu antibody, but less than a week after her death Genentech announced it would start an expanded access programme.

"I think that any company that experiments on human beings has the responsibility to at least provide some drugs to people who have no other hope," said Nelson's husband Bob Erwin. "To say, 'We're just going to let you die until we can market this drug and make our profits' – that's just morally wrong."

He now helps run the Marti Nelson Foundation/Cancer Action Now, which campaigns for more and better compassionate use schemes. Their website www.canceractionnow.org provides very helpful advice to patients seeking access to experimental drugs.

"Long-term side-effects mean nothing to me. Without treatment the only long-term effect for me is death"

Glivec – *Magic cancer bullet* – Daniel Vasella, the Novartis CEO, talks about the huge gamble he took when he decided to invest in large-scale production facilities, "providing tons of Glivec active substance and millions of capsules instead of just kilogrammes and thousands of capsules."

Unfair

What this means for dying cancer patients is that, very often, even when companies do agree to supply the investigational drug outside of a clinical trial, only some of the patients seeking access get it – depending on where they live and who is their doctor.

The growth of Internet patient networks, where patients can swap stories about what they are on and seek tips about how to get hold of potential new options, has brought to light the great disparities in the time it takes for cancer patients with very urgent needs to access investigational drugs.

In a submission to an EMEA consultation on compassionate use, Eurordis, a European advocacy group for patients with rare diseases, painted the following picture. Companies sometimes restrict compassionate use programmes to centres that agree to run their regulatory trials, "as a gift to investigators". Some companies only open programmes in Member States where they can levy a charge. Where product supply is limited, some companies distribute the drug on a first come, first served basis, which favours the best informed and those closest to the participating treatment centres or most able to travel. Other compassionate use programmes recruit at the sole discretion of physicians. Ethics committees have been known to advise setting up lotteries or other random procedures for selecting patients, rather than prioritising those in most urgent need.

EMEA guidelines

European patient advocacy groups were hopeful that this inequity would be addressed this year, when EMEA drew up its first Guideline on Compassionate Use of Medical Products, which aimed to "facilitate and improve the access of patients in the European Union to compassionate use programmes". EMEA said that it would "favour a common approach regarding the conditions of use, the conditions for distribution and the patients targeted for the compassionate use of unauthorised new medicinal products."

In the event, the Guideline, published this July, fell far short of patient community aspirations. It provides a legal basis for EMEA to issue 'an opinion' on compassionate use of an investigational drug, which would cover conditions of use (dosage, how to administer and use safely), conditions for distribution (whether subjected to special or restricted medical prescription) and target patient groups.

A disappointed Eurordis criticised the Guideline as "a missed opportunity" to tackle key inequities in the supply of drugs for compassionate use. Eurordis wants EMEA's opinion on 'conditions of distribution' to cover how much drug should be available in how many Member States, and believes that EMEA would have a better opportunity of achieving a fair compassionate use programme if it were to discuss conditions for distribution collectively with the manufacturers and all Member States together. This, they argue, would prevent companies from cherry-picking where they distribute investigational drugs and under what conditions. "25 [Member States]

EMEA guideline on compassionate use

Eligibility

The Guideline defines eligibility for compassionate use programmes as patients with "A chronically or seriously debilitating disease, or a life threatening disease … who cannot be treated satisfactorily by an authorised medicinal product".

A key stipulation is that "patients should always be considered for inclusion in a clinical trial before being offered compassionate use programmes."

Level of evidence

In considering whether a drug should be made available for compassionate use, EMEA will consider "promising early data observed in exploratory trials (e.g. uncontrolled phase II trials)".

How triggered?

EMEA may offer an opinion provided one Member State has asked for such an opinion, or if two Member States have notified EMEA that they are seeking to set up compassionate use schemes.

The full text can be found at www.emea.europa.eu/pdfs/ human/euleg/2717006enfin.pdf

Eurordis criticised the EMEA Guideline as 'a missed opportunity' to tackle key inequities

together are in a better position to negotiate … key aspects of a compassionate use programme than each of them separately."

EMEA acknowledges concerns "in respect of differential supply to Member States markets of compassionate use products", but says that its powers are restricted to scientific opinion and do not extend to market supply.

The industry, in contrast, feels EMEA is being far too bold, and a number of industry bodies indicate unease at the prospect of EMEA issuing opinions about compassionate use before establishing whether the manufacturer can or will supply the drug. The European Federation of Pharmaceutical Industries Associations (EFPIA) says: "To generate publicly available … recommendations for compassionate use in a situation where the applicant is not in a position to satisfy request for the drug would be unethical."

Under the guideline, EMEA can issue an opinion on compassionate use if one Member State requests it, or if two or more Member States notify EMEA that they are looking to set up a compassionate use programme. The industry presumably fears that, once an opinion is issued, patients and doctors in every EU country will use it to put pressure on the company to supply the drug. This is probably exactly what will happen – but as Eurordis points out, the leverage that patients and their doctors have lobbying country by country is far smaller than it would be if they all sat around the same table.

The AIDS experience

Ten years ago, Europe's AIDS patients reached a very similar conclusion. They set up the European Community Advisory Board in 1997 to give them a platform from which they could influence drug development from the earliest stage of designing a trial, through to post-approval monitoring of adverse side-effects. Early access for all European patients was a key issue for them.

ECAB was based on the concept of the community advisory boards that pharmaceutical companies set up to get advice and feedback from patients, but it had two crucial differences. It is part of an independent patient organisation, the European AIDS Treatment Group, which means that patients set their own agenda, and it gives a single voice to AIDS patients throughout Europe, which ensures that pharmaceutical companies listen to them. The board is composed of 20–30 patients who have developed expertise in the area of research and trials. They meet several times a year to discuss clinical trials and developments in the pipeline with pharmaceutical companies, and to organise training for new members.

ABIGAIL'S STORY

Abigail Burroughs died in 2003 at the age of 21 from a head and neck cancer, at a time when the first epidermal growth factor receptor (EGFR) inhibitors were in early clinical trials. Gefitinib (Iressa) was being tested by AstraZeneca for use in non-small-cell lung cancer, and cetuximab (Erbitux), developed by ImClone, was in trials for colorectal cancer. Abigail's tumour was rich in epidermal growth factor receptors, and her oncologist was very hopeful that it might respond to one of the EGFR inhibitors. Neither company, however, was willing to let her try drugs that were very experimental and were being trialled for use in other settings. In the words of her doctor, "she had the right cells in the wrong place".

After failing to show strong proof of efficacy, Iressa was refused marketing approval by EMEA. Erbitux, however, has been approved not only to treat colorectal cancer, but also subsequently for squamous cell head and neck cancer.

Following Abigail's death, her father Frank Burroughs started the Abigail Alliance to help patients like his daughter get access to drugs that might help them. The Alliance brought a law suit against the US regulator, the FDA, to try to remove all regulatory controls over dying patients seeking access to investigational drugs, on the ground that they operate "as a death sentence… in violation of the guarantee in the Fifth Amendment of the US Constitution against deprivation of life without due process".

This was rejected by an Appeals Court in August 2007. The Alliance is now pinning its hopes on changing the law through an 'Access Act', to allow companies to seek what the Alliance has called "Tier 1 approval" to market drugs to certain categories of patients with life-threatening diseases, on the basis of minimal evidence of clinical efficacy – in effect a small number of case reports. Some large and well-established patient advocacy bodies, including the US National Breast Cancer Coalition and the US National Coalition for Cancer Survivorship, are opposing the Act, arguing that it would result in the market becoming awash with drugs for which hard scientific data will never be collected.

Simon Collins has been a member of ECAB since it started, and co-chair for two years, during which time he has been involved in negotiating numerous expanded access programmes. Pressure from patients – and from doctors – he says, is essential. "If there was no pressure from patients, there wouldn't be any EAPs. It is driven by patient demand and many doctors as well." He points out, however, that not all doctors are prepared to use earlier access for their patients, sometimes for bureaucratic reasons, "With all the work that we do as advocates trying to get these programmes going, it is heartbreaking to see the blocks we get from doctors saying: 'Oh no, I don't want to do all that paperwork. I'd rather wait for approval'."

ANDY'S STORY

Andy Giusti is 42 years old and 'in excellent health' – except for the stage IV colorectal cancer he had diagnosed two and a half years ago, which will kill him if he doesn't find a therapy that works. The clock is ticking.

A biotechnology research scientist by profession, Giusti has been following developments in cancer therapies to identify something that might help him. It was almost two years ago, at a research meeting on colorectal cancer, that he first came across a DNA vaccine, Trovax, which is designed to work in all solid tumours where the 5T4 tumour antigen is present. Early results of a phase II trial using the vaccine in combination with FOLFOX and FOLFIRI (standard treatment for stage IV colorectal cancer) were presented, and looked promising. He contacted the manufacturer – a small but well-established biotechnology company in the UK – to see whether there were any new clinical trials planned that he might be eligible for, and ask about their policy on compassionate use. The answer came back that there were no new trials planned in colorectal cancer, and that all of the vaccine they were manufacturing was being used for other trials – no compassionate use programme.

"Two years have now elapsed," says Giusti. "I have seen in the news that sanofi-aventis is now partnering with Oxford BioMedica to bring Trovax forward into a phase III trial for colorectal cancer. In this time extensive safety data has been generated using this vaccine, and indications are that it still shows promise for metastatic colorectal cancer patients. However, I have now been treated with all of the chemotherapy/biologic treatments that are currently approved. Unfortunately, I still have visible disease, and because of this extensive treatment history I am not likely to meet the inclusion criteria for this upcoming phase III trial."

An active patient advocate, Giusti says he is well aware of the complex issues surrounding access to experimental drugs, but he believes companies have a duty to make an effort to help patients like himself, who have run out of options, particularly if the drug is already cleared for phase III trials and a major pharmaceutical company is involved. "Our initial efforts have not met with much success," says Giusti, "but I am hopeful that we will ultimately reach an individual at one of these companies that will open a productive dialogue about access to Trovax via compassionate use."

However, he agrees with Eurordis that manufacturer supply problems are the most common obstacle to early access. "The major block is the pace the company wants to run this programme – how soon they plan to scale up their production line sufficiently to have an expanded access programme. As soon as they have efficacy data – some of that comes from phase II – and a reasonable safety indication, we say the company should plan for scaling up the expanded access programme before they start phase III studies. We tell them that they should be planning the scale up much earlier in their production programme."

The great advantage of operating at a European level is the ability to address in a single forum issues that are common to patients throughout the 27 countries of the EU. When ECAB asks companies to scale up an expanded access programme, they ask for that programme to run all over Europe, and give feedback to the company when there are unacceptable delays. "Some countries can be very slow at getting these EAPs up and running. You can agree something with the central company, but then the Portuguese or Spanish ECAB member, for instance, may come back and say, 'Well we phoned Roche (or Merck, or whatever) locally, and they don't know anything about it.' It makes the company aware of problems with their affiliates."

Let's go!

What ECAB has done for one section of Europe's patients is to give them a voice at the table. And what patients bring to that table, above all, says Life Raft's Scherzer, is a sense of urgency. "It's always been surprising to me that the world of cancer treatment and experimental cancer treatment seems to lack a sense of urgency. I worked for many years in public health, including at the Centres of Disease Control – that world was exactly the opposite. It is a world of

LESLIE MULKEY

Delay = death. American patient advocates from the Abigail Alliance, the Cancer Cure Coalition, A Right To Live (a prostate cancer advocacy group) and the Sarcoma Foundation of America took their message to the FDA's headquarters in Rockville, Maryland, September 18th

great urgency. To some extent, I am terribly fortunate or unfortunate – I had no training for this culture and I bring to it a completely different set of values. Let's go, let's move, what's the problem? That attitude sometimes helps."

He and his Life Raft colleagues have helped countless patients seek compassionate access to investigative drugs – including drugs that are still in, or about to start, phase I trials. It is a constant search for ways to influence a system in which patients have never been invited to play a role. The Life Raft monthly newsletter is sent to as many researchers and executives as patients, and the group has a very active website. "We have the capacity to state our position. We also have a very good relationship with the media. So that gives us a bit of leverage in imposing ourselves on the system."

On one memorable occasion, Scherzer informed the head of a top hospital in Europe that he would be 'named and shamed' in their newsletter if he did not speed up the process of setting up a clinical trial, given the lives that were at stake. Scherzer was threatened with a libel suit for his trouble, but the clinical trial started the very next morning!

Life Raft is not always so successful, and after years of firefighting on behalf of dying patients, Scherzer is beginning to question why patients and patient advocates should be reduced to lobbying, cajoling or threatening from the margins.

"My philosophy is changing and I have adopted the mantra that the European Cancer Patient Coalition has developed, which is 'Nothing About Us Without Us'. I used to think it would really be something if they would even let us in the room. Then I thought, I'd like a seat at the table and I would like it to be one of those decision-making seats. And now I have adopted probably the most controversial point of view. I think I should be sitting at the head of the table running the meeting, because I am the only one in the room for whom the needs of the patient are in fact the first and paramount priority."

Controversial with some perhaps, but this was of course precisely what the European AIDS patients did when they set up ECAB, which has served them well. And given that EMEA has now made it clear its influence over compassionate use will extend no further than presenting an opinion, Europe's cancer patients could find such a table just the forum to exert pressure for compassionate use schemes to be set up early and equitably across all Member States.

"I should be at the head of the table … I am the only one for whom the needs of the patient are paramount"

Breast screening:
a question of pros and cons
not right or wrong

Marc Beishon

Decades after breast screening programmes first started, their value remains hotly disputed. Some lives are saved, but it's hard to tell how many. False-positives are a problem, but it's a risk some are happy to take. Women need to weigh up for themselves the pros and cons of attending screening – but they can only do so if they are given clear, unbiased information.

In June 2002, a Global Summit on Mammographic Screening was convened in Milan to examine the controversy created by a *Lancet* article and a Cochrane review, which suggested there was no evidence to support the efficacy of breast screening to reduce cancer deaths. The summit, chaired by Umberto Veronesi, was one of several groups looking again at the data on breast cancer screening, and the stir created by the Cochrane reviewers was by no means the first to ripple through the screening community.

But the conclusions from the summit and from many commentators afterwards were unequivocal – mammographic screening was effective. As Peter Boyle, now head of the International Agency for Research on Cancer (IARC), which re-examined the studies, wrote in an editorial in the *Annals of Oncology*, "Taking all the criticism into account, it was still possible to conclude that screening mammography reduced the mortality from breast cancer in women receiving an invitation to be screened in well-organised clinical trials: the reduction in breast cancer mortality appeared to be between 21% and 23% according to recent estimates. There were no grounds for stopping on-going screening programmes nor planned programmes."

The phrase most widely used was: "It's time to move on." But the Cochrane reviewers have continued to update their study and the latest version (published in 2006) still reaches more or less the same conclusion: "It is not clear whether screening does more good than harm." Given the Cochrane Collaboration is one of the most widely respected sources of systematic reviews, the controversy about mammographic screening is still very much an issue – as evidenced by a very public confrontation over an article withdrawn in 2006 from publication in the *European Journal of Cancer* that examined further (and criticised) the quality of data in one of the key screening trials, the Swedish two-county trial (the paper has since been published by the *Danish Medical Bulletin*).

Peter Gøtzsche and Ole Olsen (Margrethe Nielsen in the 2006 update) are the two Denmark-based Cochrane authors, and it is important to note that their review is only of randomised controlled trials that compared women invited to screening with non-invited controls, and that there are relatively few (seven met the inclusion criteria), and most were started some time ago (one as far back as 1963). There are many points made about methodological weaknesses, not surprisingly as trial methods have evolved for the better, but as Gøtzsche comments there are two key issues that stem from their analysis.

"Only half of detected DCIS progress to invasive cancer, and inevitably there is unnecessary intervention"

Questionable data

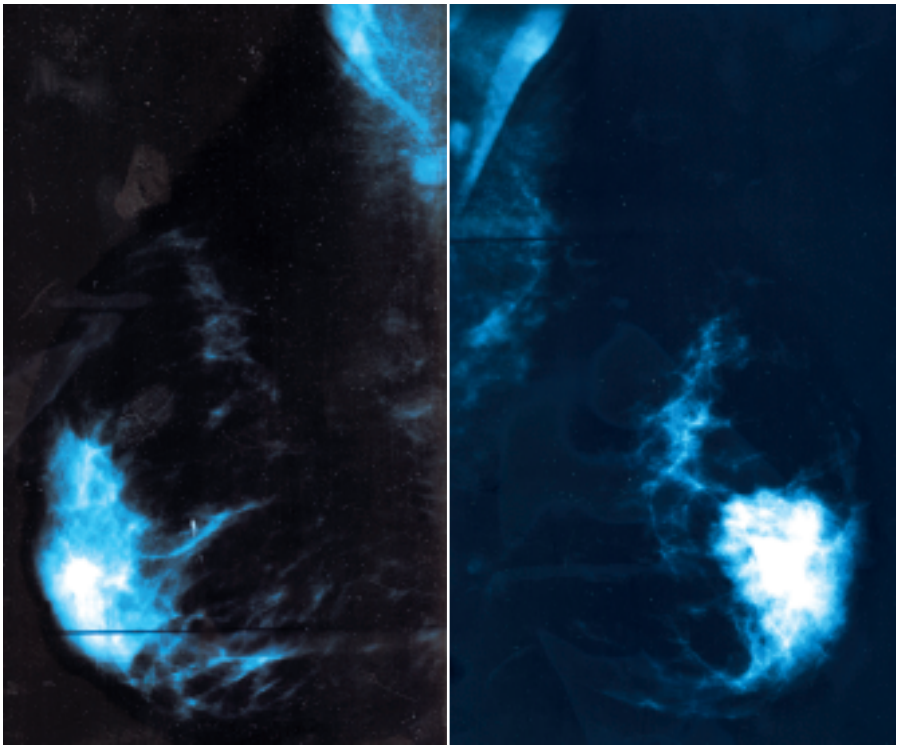
The first is that judging the main outcome target of the trials – assignment of death from breast cancer – is "unreliable and biased in favour of screening". The two best trials (in terms of the quality of randomisation) in fact showed no benefit. "Also, no mortality benefits were shown for overall mortality and all cancer mortality, which is interesting as misdiagnosis of death often concerns other cancers," says Gøtzsche. In other words, they called into question breast cancer mortality as an outcome.

The other big issue he raises is overdiagnosis. This applies especially to ductal carcinoma in situ (DCIS) – only detectable by conventional mammography or other techniques such as MRI – and also to slow-growing and benign cancers. Gøtzsche says he was surprised that the issue of overdiagnosis and overtreatment had not been more widely discussed before it was raised in his *Lancet* article, and notes that only half of detected DCIS progress to invasive cancer, and that inevitably there is unnecessary intervention.

"I'm still worried that it is not possible to see an effect on cancer mortality as such, but it would be unexpected if there was no effect at all measured by the trials. We do think there is a minor effect of screening. We don't know exactly how big it is, but we have come up with an estimate, a 15% relative risk reduction, which is close to the US Preventive Services Task Force estimate of 16%. So personally I think it is a realistic guess."

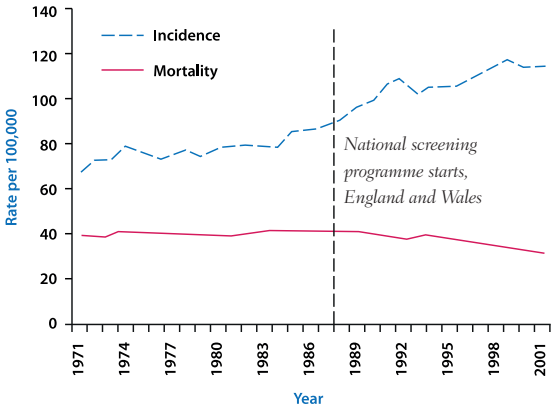
As Gøtzsche and Nielsen report, their 15% estimate translates into the estimate that for every 2,000 women invited for screening over 10 years, one will have her life prolonged but 10 healthy women will be unnecessarily diagnosed as cancer patients and treated unnecessarily. Gøtzsche qualifies the 15% figure by pointing out it is for all ages in the trials, not the higher-risk older groups, as the differences between the age groups were relatively minor. The US Taskforce found 'fair evidence' that mammography screening every 12–33 months significantly reduces mortality from breast cancer, especially in the 50–69 age group.

Most other reviewers, including the US Task Force and the IARC, consider that the quality of the trials has come in for unjustifiable criticism by the Cochrane reviewers, and there are many other types of study, such as national comparisons of age cohorts, that have added to the evidence base in favour of screening. The IARC's estimate of a 25% reduction in mortality in women first invited for screening between the ages of 50 and 69, based on an intention to treat analysis, implies a 35% reduction for women who are screened regularly, and is widely quoted.



Misleading. Mammography can be particularly unreliable for women with dense breast tissue. These images were not interpreted as suspicious, but cancer was detected by ultrasound three months later

MAKING SENSE OF THE STATISTICS



Following the introduction of the national screening programme in England and Wales, more women are being diagnosed with breast cancer but fewer are dying of it. Does this show that screening saves lives through earlier detection? Or is mammography simply identifying lesions that would never have gone on to become invasive cancers? And how much of the improvement in survival is due to the introduction of tamoxifen?

Source: UK National Statistics, 2005

What does seem to be emerging now is a stronger consensus that widespread screening for women in the 40–49 age range is not worthwhile, mainly as breast density creates a high false-positive rate and the mortality risk in this group is lower than for older women. This year, the American College of Physicians revised its recommendations from regular screening to advising women to talk to their doctors about whether a mammogram is suitable for them. In the UK, one of the few recent randomised trials, the 'Age' study, has recently reported no significant benefit for this younger age group (Gøtzsche describes this as a 'fine trial' and says it will be added to the Cochrane review). Sue Moss, who runs the UK Cancer Screening Evaluation Unit at the Institute of Cancer Research, says that follow-up with a better powered study will be done. Some countries and regions in countries, advocacy organisations such as the Susan G Komen for the Cure in the US, and bodies such as the American Cancer Society, continue to recommend regular screening from the age of 40.

More attention is now focused on the older, 50–70 years, age group. This is the target for the UK's NHS Breast Screening Programme, which has been screening 1.3 million women a year – about 75% of those invited – according to a 2006 report. This notes that for every 400 women screened regularly over 10 years, one fewer will die, and about 1,400 lives are being saved a year (and this is one of the main public messages of the programme). This is much higher than the Cochrane reviewers' estimate – about five times – and also shows the scale of the gap.

Stephen Duffy, professor of cancer screening at Queen Mary, University of London, and Cancer Research UK, says there are robust data to support the higher benefit. "From empirical data in both randomised trials and service screening programmes, our group has estimated that the benefit of being screened, as opposed to simply being invited to screening, was of the order of a 30–40% reduction in breast cancer mortality. This translates to one life saved per 400–500 women screened over 10 years. This bears out the estimates quoted for the UK programme."

The reasons for the much lower estimates of benefit quoted by others are, he adds, "reliance on guestimation based on personal judgements of the quality of the studies rather than the actual data, the confusion of invitation to screening with actually being screened [typically 25%–30% of those offered screening in the UK do not take it up], and the confusion of period of follow-up with period of screening." Duffy also considers the unreliability of mortality data to be a "red herring" and, as a researcher involved with the Swedish two-county trial and others since the late 1980s, can provide a battery of co-authored papers that address this and other issues such as overdiagnosis.

Practising radiologists tend to be much more circumspect (in part because they have been put on the defensive, considers Duffy). Robin Wilson, a consultant breast radiologist who chairs the NHS's screening radiology coordinating committee in the UK, and is also the screening representative of the European Society of Mastology, is if anything even more critical than Gøtzsche about the quality of the main screening trials. "The truth is the quality of the mammography in the New York trial [the oldest one] was awful, and there were all sorts of flaws in the data and designs of the studies," he says.

"What we do know is that breast cancer mortality has fallen by about 25% in the last 15 years, but of course you cannot attribute all that to screening. It is a combination of screening and better treatment, in particular the use of tamoxifen." A UK study reporting on a 21% reduction in death from breast cancer attributed 6.4% of the 21% to screening, the rest to better treatment and earlier diagnosis independent of screening. "Bear in mind this was

Some countries still recommend screening from age 40

"It is a combination of screening and better treatment, in particular the use of tamoxifen"

early on in the screening rollout, and we knew we were not seeing the full effect," says Moss.

Another factor in recent years is the impact of warnings about hormone replacement therapy (HRT) and its association with breast cancer. In the US, a study reported rising breast cancer incidence until the take up of mammography levelled off, and then a decline, with a big decrease in 2002–2003, which is probably attributable to less use of HRT. Attempts have also been made to distinguish between the effect of screening and adjuvant therapy on mortality – a US consortium came up with a wide range – the total mortality reduction contributed by screening varied from 28% to 65%, with adjuvant treatment contributing the rest.

Improving quality of care

For Wilson, the actual impact of screening on its own is of less importance than its contribution to the overall standard of care and treatment. "It is true that it does not save as many lives as we thought it would, but if you look at countries that have screening and compare them with those that don't, the standard of care is usually much higher in the former. In the UK it has helped improve care out of all recognition – and we also see big differences in standards between units that carry out screening and those that just offer symptomatic breast care."

Wilson notes that a revision to the NHS cancer strategy will recommend that symptomatic breast investigations should only be done in centres where screening is carried out. As he adds, there are only 105 screening centres in the UK, but some 3000 in France, which are mainly office-based units, where the only solution to keeping them going has been to send results to central locations for reading. If quality of screening is often raised as an issue in Europe, it is certainly a big problem in the US – as many as 40% of facilities there have been cited for violating federal rules, according to Madelon Finkel in her book *Understanding the Mammography Controversy*.

Jayant Vaidya, a consultant breast surgeon in Dundee, Scotland, who worked with one of screening's greatest critics, Michael Baum, reckons that we should be seeing a steeper mortality decline in the UK, thanks to its structured screening programme, than the US, where screening is "haphazard". "But the slope of decline is not very different," he says.

Early – or rather earlier – detection is the goal of breast screening, but it has led to a large increase in reported cancer incidence and problems with overdiagnosis and overtreatment. "By the time a mammogram detects a cancer it can be already half a centimetre in size and may have lived more than half its lifetime, and can have metastasised," says Vaidya. "Others won't be growing but we don't know which ones."

Treatment of DCIS – very rarely detected before mammography – is fraught with controversy. The US National Cancer Institute (NCI) simply notes: "DCIS can progress to become invasive cancer, but estimates of the likelihood of this vary widely." Vaidya points out that screening mammography does not seem to have reduced the incidence of invasive cancer. Moss says, however, "If you talk to pathologists they say most of the DCIS that gets picked up by screening is high grade."

False-positives

False-positive and overdiagnosis rates vary – they are high in the US, where there is a litigation culture, and of course mammograms also miss cancers. Misleading women about the accuracy of screening was the leading cause of medical negligence claims in the US, according to a 2006 book, *The Death of Mammography*, by Rene Jackson and Alberto Righi, which notes that 700 mammography facilities have shut in recent years. The NCI, in summarising harms of mammography in its Physician Data Query (PDQ) database, currently cites evidence that about a third of screen-detected cancers represent overdiagnosis, half of women screened annually for 10 years will have a false-positive (and a quarter will have biopsies), and 6%–46% of women with invasive cancer will have negative mammograms, especially younger women.

Says Duffy, "Our research on actual screening data arrives at lower estimates of overdiagnosis than those of some colleagues." Wilson considers the rate of overdiagnosis to be more like 9%–10%. "We don't know which ones are harmful, but if you say you have a 30% chance of developing a cancer that kills, very few people will take a risk and not have treatment. Further, very few women complain about being called back – obviously they are worried but they are mostly aware that one in nine of them will get breast cancer." He notes a study that

"Much more information about the balance between benefit and harm should be given to women"

shows that women will tolerate a high false-positive rate.

Both he and Gøtzsche agree that much more information about the balance between benefit and harm should be given to women. "We need to be much more honest about the downsides," says Wilson. Gøtzsche, with co-author Karsten Juhl Jorgensen, examined the content of invitations to public screening programmes in a 2006 *BMJ* paper, finding that while information about screening was often provided, it tended to mislead on benefits – such as giving relative, not absolute, risk reductions and not pointing out they apply only to the screening period and not to a lifetime. It was also unclear on the most important harms, with overdiagnosis and over-treatment not mentioned, and other harms "omitted or downplayed".

The important bond between doctor and patient is being bypassed by playing on fear of cancer and setting up appointments that imply a public duty to attend, says Gøtzsche. And of course women invited for screening are not patients – they are healthy citizens, at least for breast cancer. "This I think is the crux of the breast screening debate – the way it is being sold to the public is deeply unethical," he says. In short, Gøtzsche, who says he has received many personal attacks about his work, feels the tension between advocates and critics is still great, at least politically. As Duffy comments, "It is also sad to see the morale of the staff providing the service damaged by unduly pessimistic publications on the subject."

But has the debate moved on? The original *Lancet* paper by Gøtzsche and Olsen called mammography screening "unjustified". Now their message has moderated – it is "unclear". Most responsible advocates of screening are not making highly inflated claims, and warn against complacency in intervening with such large populations.

The uncertainty in this highly complex area is well reflected in most presentations, such as the NCI's PDQ guidelines (although the NCI itself recommends screening from age 40), and on breast charity websites, but it does have to be searched for. Indeed, another large US advocacy organisation, the National Breast Cancer Coalition (NBCC), considers that the "mortality reduction associated with mammography screening is modest, at best … NBCC believes that there is insufficient evidence to recommend for or against screening mammography in any age group of women." In the UK, there has been a move to promote all screening more by choice and informed consent than by herding people blindly in one direction.

Vaidya, who concurs with Wilson that screening has been pivotal to better organisation of cancer services, considers that it is not realistic to think that screening will be abandoned. The way forward, he believes, is through more research on new tools that can differentiate the harmful from the harmless.

That, at least, is something everyone can agree on.

Public duty or personal choice?

Is surgery necessary following chemoradiation for patients with locally advanced cancer of the oesophagus?

Dirk Rades and Steven Schild

A landmark study has shown that patients with locally advanced epidermoid cancer of the oesophagus who respond well to induction chemoradiotherapy do not benefit from subsequent surgery and, therefore, seem to be well treated with definitive chemoradiotherapy.

Locally advanced oesophageal cancer carries a poor prognosis, and its treatment presents an interdisciplinary challenge. Therapy generally involves neoadjuvant chemoradiotherapy followed by surgery or definitive chemoradiotherapy. Chemoradiotherapy has been proven to be superior to radiotherapy alone. The role of surgery has been challenged because of the poor outcome following resection alone and mortality rates of up to 15% after surgery preceded by chemoradiotherapy. It may be questioned whether all patients with locally advanced oesophageal cancer need surgery or whether certain subsets of patients are well treated with chemoradiotherapy alone, which is associated with lower treatment-related mortality than chemoradiotherapy followed by surgery.

Bedenne et al. addressed this question in a phase III trial (see opposite) that included 259 patients (230 with epidermoid cancer; 29 with adenocarcinoma) who responded well to two cycles of induction chemoradiotherapy with cisplatin and fluorouracil. Radiotherapy was performed as conventional (46 Gy over 4.5 weeks) or split-course (15 Gy on days 1–5 and 22–26) treatment. Patients were randomly assigned to receive either further chemoradiotherapy (three cycles of cisplatin and fluorouracil, and 20 Gy conventional or 15 Gy split-course radiotherapy) or surgical resection. The three-month mortality rate was higher with resection than with chemoradiotherapy alone (9.3% vs 0.8%, P=0.002). Surgery resulted in better locoregional control (hazard ratio for further chemoradiation vs surgery 1.63; P=0.03), but was not associated with a significantly better median survival time (17.7 months after surgery vs 19.3 months after definitive chemoradiotherapy) or two-year survival rate (34% vs 40% respectively; P=0.44). These results are consistent with the data from a randomised trial reported by Stahl et al., in which patients with locally advanced squamous cell carcinoma of the oesophagus who had received induction chemotherapy followed by chemoradiotherapy were randomly assigned to receive either surgery or additional chemoradiotherapy. Locoregional control at two years was better after surgery (64% vs 41%; P=0.003), whereas survival was not significantly improved.

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Bedenne and co-workers concluded that patients who respond well to induction chemoradiotherapy do not benefit from resection. The results might have been confounded by methodological issues, however. Patients who had resection received an overall lower dose of chemotherapy, which could have negatively affected outcome. Also, in most other oesophageal cancer studies, staging did not include endoscopic ultrasound. Another problem is the use of split-course radiotherapy, which is associated with significantly worse survival rates than conventional radiotherapy.

Although both treatment groups were balanced regarding the radiotherapy treatment received, the risk of a selection bias still exists because the results were not stratified by radiotherapy regimen. Furthermore, when the study was conducted, it was not recognised that haemoglobin levels before and during chemoradiotherapy are significantly associated with treatment outcome. Maintaining haemoglobin levels at 12.0–14.0 g/dl during chemoradiotherapy could improve outcome by facilitating better tumour oxygenation and enhanced radiosensitivity.

Despite its methodological problems, the study reported by Bedenne et al. is a landmark. It alerts clinicians to be more restrictive in the use of resection for locally advanced oesophageal cancer. This advice is particularly relevant to patients who respond well to induction chemoradiotherapy or have relevant pre-existing comorbidity. In the study reported by Bedenne et al. 89% of patients had epidermoid cancer, so the findings might not be applicable to other histologies.

Details of the references cited in this article can be accessed at www.cancerworld.org/cancerworld

Synopsis

L Bedenne, P Michel, O Bouché et al. (2007) **Chemoradiation followed by surgery compared with chemoradiation alone in squamous cancer of the esophagus: FFCD 9102.** *J Clin Oncol 25:1160–1168*

Background. In patients treated with chemoradiation for oesophageal cancer, uncontrolled studies have reported similar survival rates in those treated with or without the addition of surgery.

Objective. To demonstrate in a randomised trial that patients who respond to initial chemoradiation have equivalent overall survival after chemoradiation alone to after chemoradiation followed by surgery.

Design. Between February 1993 and December 2000, this randomised trial recruited patients with resectable T3N0–1M0 epidermoid cancer or adenocarcinoma of the thoracic oesophagus who were candidates for surgery and radiation. Exclusion criteria were as follows: tumour within 18 cm of the dental ridge; tracheobronchial, supraclavicular node or gastric cardia involvement; visceral metastases; weight loss >15%; symptomatic coronary heart disease; Child–Pugh B or C liver cirrhosis; or respiratory insufficiency.

Intervention. All 444 eligible patients received induction chemoradiation consisting of two cycles of cisplatin and fluorouracil and either conventional (46 Gy over 4.5 weeks) or split-course (15 Gy on days 1–5 and 22–26) radiotherapy planned to include the macroscopic tumour and adjacent lymph nodes. Each cycle of chemotherapy comprised fluorouracil (800 mg/m^2 daily for 5 days) as a continuous intravenous infusion and cisplatin (15 mg/m^2 daily for 5 days) as a 1 h intravenous infusion. Response was assessed using endoscopy, biopsies, oesophagogram, chest and abdominal CT, and (if available) endoscopic ultrasonography, and only responders were considered for the randomised section of the trial. Patients in arm A underwent surgery but no further chemoradiation. Patients in arm B received a further three cycles of chemotherapy and either 20 Gy of conventional or 15 Gy of split-course radiotherapy.

Outcome measures. The primary outcome measure was overall survival. Secondary outcome measures were type of recurrence, duration of stay in hospital, quality of life and procedures required for treatment of dysphagia.

Results. Among the patients who responded to induction therapy, 129 were randomly assigned to arm A and 130 to arm B. For arms A and B, median survival times were 17.7 and 19.3 months, respectively, while two-year survival rates were 34% and 40%, respectively. The frequency of metastases was not different between the arms, but there were more locoregional relapses following chemoradiation alone than after chemoradiation plus surgery (hazard ratio for arm B versus arm A 1.63; 95% CI 1.04–2.55; P=0.03). The three-month mortality rate was higher (9.3% vs 0.8%; P=0.002) and the duration of hospital stay was longer (68 days vs 52 days; P=0.02) in arm A than in arm B. A procedure for dysphagia was required in 24% of patients in arm A versus 46% in arm B (P<0.001). Quality-of-life analysis showed no difference between the two arms.

Conclusion. The addition of surgery to chemoradiation does not improve survival or quality of life in patients with locally advanced thoracic oesophageal cancer who respond to initial chemoradiation.

Acknowledgement: The synopsis was written by Petra Roberts, Associate Editor, *Nature Clinical Practice*.

Is rituximab maintenance therapy useful following rituximab salvage in refractory or relapsed follicular lymphoma?

David Ritchie

A study by the German Low Grade Lymphoma Study Group has shown that rituximab maintenance following salvage with rituximab-containing chemotherapy is the standard of care for advanced-stage refractory or relapsed follicular lymphoma.

Rituximab maintenance therapy following chemotherapy for follicular lymphoma (FL) is the latest permutation in the application of anti-CD20 monoclonal antibody immunotherapy.

Studies of rituximab added to chemotherapy regimens including CVP (cyclophosphamide, vincristine and prednisolone), FCM (fludarabine, cyclophosphamide and mitoxantrone) and CHOP (vincristine, doxorubicin, prednisolone and cyclophosphamide) have revealed improvements in response rates, disease-free survival and overall survival in advanced-stage FL either initially or at relapse. Studies have now established that rituximab maintenance therapy after salvage chemotherapy, rather than traditional observation alone, also delivers substantial clinical benefit.

Forstpointner et al. report, on behalf of the German Low Grade Lymphoma Study Group (GLSG), the impact of rituximab maintenance following rituximab-FCM (R-FCM) therapy in patients with relapsed or refractory FL or mantle-cell lymphoma (MCL). Strikingly, the addition of rituximab maintenance resulted in marked prolongation of response duration in both lymphoma types, with the greatest impact seen in patients with FL (median response duration not reached vs 26 months for observation only; P=0.035). Whilst clearly beneficial compared with observation alone (median response duration 14 months vs 12 months; P=0.049), the results of rituximab maintenance in MCL are less marked than those achieved by aggressive chemotherapy regimens, such as rituximab plus Hyper-CVAD (fractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone) alternating with rituximab plus methotrexate–Ara-C (cytarabine). The results reported by Forstpointner et al. in FL are, however, supported by similar recent findings from a European Organisation for Research and Treatment of Cancer Intergroup study, which randomised patients with recurring FL to salvage therapy with CHOP or rituximab-CHOP, followed by a second randomisation to observation or maintenance rituximab (as a single infusion every three months for two years).

The central finding in both the GLSG and the Intergroup studies is that a long-lasting advantage can be achieved with rituximab maintenance – even when the salvage regimens contained rituximab – resulting in the dual benefits of disease control and a reduction in the number of chemotherapy regimens required over time.

Furthermore, the study by Forstpointner et al. confirms the Intergroup findings of no discernable pattern of increased toxicity, promotion of resistant FL subclones or alteration in the

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Synopsis

R Forstpointner, M Unterhalt, M Dreyling et al. (2006) **Maintenance therapy with rituximab leads to a significant prolongation of response duration after salvage therapy with a combination of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) in patients with recurring and refractory follicular and mantle cell lymphomas: results of a prospective randomized study of the German Low Grade Lymphoma Study Group (GLSG).** *Blood 108:4003–4008*

Background. Treatment with a combination of rituximab and chemotherapy improves prognosis in patients with follicular lymphoma (FL) or mantle-cell lymphoma (MCL).

Objectives. To establish whether, in patients with recurrent or refractory FL or MCL, rituximab maintenance therapy is beneficial following induction of remission by rituximab in conjunction with a chemotherapy regimen.

Design. This prospective, phase III, randomised, open-label, multi-centre trial by the German Low Grade Lymphoma Study Group (GLSG) included adult patients with FL or MCL who had experienced lack of response to or relapse after chemotherapy and disease recurrence following autologous stem cell transplantation. Patients who had received rituximab as part of their chemotherapy regimen were not excluded. Women who were pregnant or lactating or who were of childbearing potential were excluded. Patients were enrolled between November 1998 and April 2005.

Intervention. Patients received an induction regimen consisting of the following: rituximab (375 mg/m^2 of body surface area) on day 0, fludarabine (25 mg/m^2/day) intravenously over 30 min. on days 1–3, cyclophosphamide (200 mg/m^2/day) as a 4 h infusion on days 1–3 and mitoxantrone (8 mg/m^2) intravenously over 30 min. on day 1 (R-FCM). A small number of patients received FCM alone. Patients in either group who then achieved a complete or partial response were randomised to rituximab maintenance therapy or to no further treatment. The patients who were randomised to rituximab maintenance received two courses of rituximab (four times weekly) 3 and 9 months after completion of salvage therapy.

Outcome measures. The effects of rituximab maintenance on the relative risk of relapse were studied.

Results. Of the 195 patients randomised to rituximab maintenance or no further treatment following response to R-FCM or FCM, reference histology showed 113 patients (58%) to have FL, 66 patients (34%) to have MCL and 16 patients (8%) to have other subtypes of lymphoma. Among the 176 evaluable patients, all patients in the rituximab maintenance arm had a longer duration of response than the patients who received no maintenance. The median response duration was estimated at 17 months for patients receiving no further treatment but was not reached for the group receiving rituximab maintenance ($P<0.001$). This benefit of rituximab maintenance remained when the analysis was restricted to patients who had received initial R-FCM therapy ($P=0.035$ for patients with FL and $P=0.049$ for patients with MCL). The percentages of patients alive at three years were estimated as 77% after rituximab maintenance therapy and 57% after no maintenance therapy ($P=0.100$). Median survival time had not been reached by the time of evaluation in either study arm. Rituximab-related side-effects were generally mild to moderate. One patient in the rituximab maintenance arm had a severe allergic reaction, requiring early discontinuation of rituximab.

Conclusions. Rituximab maintenance is a promising therapy for patients with MCL or FL.

Acknowledgement: The synopsis was written by Petra Roberts, Associate Editor, *Nature Clinical Practice.*

rates of large cell transformation or extra-nodal progression with rituximab maintenance.

Some questions do remain unanswered, including which rituximab maintenance schedules are most clinically efficacious. In addition, it is unknown whether rituximab maintenance will deliver the same rates of disease control when given after rituximab-containing frontline therapy. Similarly, the ability of patients to be successfully salvaged by chemotherapy and/or autologous stem cell transplantation if their disease progresses whilst on rituximab maintenance is entirely unknown.

The challenge now is to construct algorithms for cost-effective treatment that encompass these data. Useful risk stratification can be provided by the Follicular Lymphoma International Prognostic Index, which has shown applicability in determining the depth and durability of responses to chemotherapy alone and with rituximab. The addition of rituximab maintenance, however, seems to benefit patients across all subgroups of the prognostic index and flattens its detrimental prognostic impact, suggesting that rituximab maintenance may be of benefit in all patients despite their risk stratification at diagnosis or relapse.

Details of the references cited in this article can be accessed at www.cancerworld.org/cancerworld

The passion behind big cancer projects

Peter McIntyre

Kris Vantongelen, now managing director of the Breast International Group, has played a pivotal role in two arenas that have been essential to the progress of oncology in recent decades: the development of systems for data collection and analysis, and the organisation of international interdisciplinary collaboration. She describes herself as 'a believer'.

Looking back, Kris Vantongelen takes a tough line about her own merits and credibility. "What was my knowledge?" she asks about setting up the first quality assurance programme in European cancer research trials. "Who were we to come and judge them?" she recalls some researchers asking on one of her visits to European hospitals. "I had no idea where to start," she says about the first conference she organised.

She is almost forensic in scrutinising her own qualities, mentioning more than once her lack of formal medical training. Yet she also describes herself as "addicted to a challenge". Her first instinct is to question whether she is the right person for the job – her second is to learn to do it.

Her rule of life is, "Passion should be the driver for everything you do, even though it's not necessarily a guarantee that you can do everything well."

She has left her mark on the development of cancer research in Europe in three ways. She worked alongside Emmanuel van der Schueren, one of the driving forces in building international collaboration and research in Europe, to develop quality control of data collection in clinical trials.

As conference and programme manager of the Federation of European Cancer Societies (FECS), she put together a succession of ECCO conferences and developed the FECS conference unit that brought a string of specialist meetings into being.

Today, she is managing director of the Brussels-based Breast International Group (BIG), managing the process of collaborative research into breast cancer work across continents.

She has done her share of writing papers and speaking at conferences, but for the most part Vantongelen has worked as a catalyst, facilitator and manager, bringing ideas to life and making things happen.

Martine Piccart, President of the European Organisation for Research and Treatment of Cancer (EORTC), recruited her to run BIG from her base at the Jules Bordet Institute in Brussels in 2006, because of her "truly remarkable skills".

"Kris immediately understands where the key cancer projects are and which deserve to be supported," says Piccart. "She brings talented people together and helps them to build a great educational conference or innovative research protocol.

She has a good feeling about what is achievable and makes it happen, and she can develop a project step by step, helping to overcome all human and bureaucratic obstacles."

Vantongelen graduated in 1968 from the Leuven Catholic University, during a tumultuous year in which student radicalism and the increasingly fractious divisions in Belgian society collided. She met her husband to be, Jos Van Grunderbeeck, as a student and they married soon afterwards. In 1969, a young married graduate in management studies, she needed a job with security and a future.

The director of Leuven University Hospital, Gerard van der Schueren (Emmanuel's father), was looking for someone with knowledge of statistics to organise the data in his oncology department. Van der Schueren was unworried that Vantongelen professed a complete lack of knowledge of medicine. He told her to join any medical course that interested her.

She jumped at the chance. "I did part of the training that radiotherapy oncologists followed and I followed the training that the nurses in oncology had from the head of the department.

"What made it so fantastic was I was 100% supported by the medical staff – multidisciplinary mentors who helped me understand how to benchmark research and the clinical implications.

A PASSION TO KNOW

"For me it became a passion to know. It was a puzzle that at first looked like 1,000 pieces. The more I learned, the more I realised that it was perhaps a 10,000 piece puzzle. It was an unbelievable opportunity and a great learning experience."

PETER MCINTYRE

Thinking BIG. Vantongelen with (left) Martine Piccart, chair of the Breast International Group, and (centre) Eleanor McFadden of Frontier Science, which does the randomisation and statistical work for BIG

Vantongelen developed a system from scratch, later taken over by the hospital registration system, to allow doctors to analyse retrospectively what had happened to the patients they treated for cancer. "We had no computer in the early '70s and developed a manually searchable database including patient and tumour characteristics, pathology, treatment and follow-up data. It is amazing thinking of that now."

In the late 1970s, Emmanuel van der Schueren became head of radiation oncology at Leuven in succession to his father, and prospective clinical trials were introduced. He asked Vantongelen to manage the protocol for the H5 trial in early-stage Hodgkin's disease – their first multi-centre prospective study.

"They said, 'You learn the protocol by heart and tell us what we need to do.' Now what does that mean? What is a protocol? What are the issues involved in conducting cancer clinical trials at a local level?" These were all things that she had to work out and learn.

Later Vantongelen acquired a computer, "like a monument, huge and very heavy", and began to devise systems to make data collection and analysis easier.

The introduction of clinical protocols required careful attention to the documentation of treatment, response and toxicity in the patient file, but consistency was difficult to achieve because doctors often had their own way of classifying symptoms and side-effects. During the 1980s, as computerisation made comparisons easier, Vantongelen became increasingly aware of discrepancies.

"I was really intrigued by the difference in interpretation of protocol guidelines and instructions between medical staff. For instance, variations in defining the dominant site of the disease, a key

She developed a system from scratch to allow doctors to analyse what had happened to their patients

Consistency was difficult because doctors had their own way of classifying symptoms and side-effects

stratification in metastatic breast cancer trials, was one of these issues that gave rise to serious concern. I mentioned this to the medical staff and asked what I could do to guarantee that what I was transferring was correct." Vantongelen organised a test amongst investigators attending the EORTC Breast Group, and this confirmed the lack of consistency in determining the dominant site of disease.

By the mid-1980s, EORTC was coordinating 200 multi-centre clinical trials across Europe, supported by a core grant from the American National Cancer Institute (NCI). The NCI warned EORTC that it would not continue financial support without quality assurance procedures. Vantongelen was asked to set up a data quality control system for EORTC and produce a report within six months that would satisfy the NCI.

With little guidance on how to devise a system that would work for researchers at different sites using many different protocols, Vantongelen used "common sense and my own experience" to set up a two-stage data quality control procedure, using a questionnaire followed by on-site visits.

With Nicole Rotmensz from EORTC, she visited hospitals, comparing their records with data on trial case report forms. The original concern was whether data were being accurately recorded. They found few errors. However, up to 14% of entries could not be checked as they were not in the patient notes.

"If the data are not in the patient's file, the origin can still be a trustworthy source, like the doctor himself, but if you cannot check it in the file you have to take it on trust. If the doctor filled the form in front of the patient that is one story. But if he did it retrospectively at the end of the week, or perhaps even later, that was a concern."

Alarming variations

Vantongelen and Rotmensz found a lack of systematic recording and alarming variations in the way that chemotherapy regimens were being implemented, especially the sequencing and intervals of drugs. Since many trials were concerned with the toxicity of treatments, with subtle but important differences between regimens, the quality of toxicity data in particular was critical.

In one year, Vantongelen and Rotmensz visited 56 hospitals in Europe and their work led directly to an improvement in data collected for clinical research. They did not always feel welcome. "In the very first visits, it looked to most investigators like we were the police coming to judge them. But trust was gradually built, supported by encouraging results."

The first findings, published in the *European Journal of Cancer Clinical Oncology* in 1989, recommended "good local organisation with tight internal control".

With a group of medical oncologists, Vantongelen devised a system to ensure the integrity of research results, with a check list for every patient entering EORTC clinical trials. However, "tight internal control" was not always easy to achieve. "The introduction of clinical trials induced a lot of extra work. Most hospitals did not have proper support systems for data and clinical research management. If the investigator was the only one to deal with all that, the administrative burden became a problem."

However, she says, "Over the years, quality assurance programmes developed for radiotherapy, chemotherapy and even for surgical procedures, together with more precise documentation of these processes. Undoubtedly this had a beneficial impact on quality of treatment, not only restricted to patients in clinical trials."

Vantongelen was increasingly in demand as a speaker about quality control at ECCO and the European radiology and oncology society, ESTRO, and at meetings of the American Society for Clinical Trials. In 1989, Rotmensz, Vantongelen and Josette Renard, from the EORTC data centre, published a book on data management and clinical trials. Further international work included a visit to MD Anderson in Houston to evaluate data management in clinical trials at the radiation oncology department.

Now chairing the EORTC data management group, Vantongelen set up training courses to bring nurses, doctors and administrators into clinical trial management – and to introduce new researchers to EORTC procedures. She produced, with Jean-Claude Horiot, from Dijon, the first written practical guide to EORTC studies, and followed this with the first edition of the EORTC manual on clinical research in breast cancer.

In 1988, it was decided to hold the 1991 EORTC European Breast Cancer Working Conference in Leuven, and Vantongelen 'volunteered' to organise it with a small team of people in the oncology department. "I had no idea where to start, but I was addicted to challenges, and this was something new. I know now that I am stress resistant. We did it and it was one of the best EORTC Breast Cancer Conferences. But I remember my words on the last day when everybody left. I said, 'Never, ever again in my life will I organise a conference.'"

By 1994 Leuven University Hospital had outgrown its city centre site, and the oncology department moved to the Gasthuisberg campus. As Vantongelen started to pack into boxes 25 years of history, she decided it was time to move on. "I thought: What would I like to do now? I only know about oncology, but I am not a specialist in anything particular."

Organising ECCO

Emmanuel van der Schueren had been a leading light in the formation of the Federation of European Cancer Societies (FECS), originally run from the same Leuven University corridor. FECS was looking for somebody to put together scientific programmes for its ECCO conference.

For the next 12 years, Vantongelen planned and organised scientific programmes for ECCO, the largest cancer conference in Europe, covering not only medical oncology, surgery and radiation oncology, but also pathology, basic science, nursing and every aspect of multidisciplinary working. The scientific committee assigned someone to be responsible for the programme, assisted by experts from other disciplines. Synergy with the committee and the chair was crucial for achieving an interesting and balanced programme. "It was a fascinating time. I knew a lot of people and we were very complementary."

Vantongelen worked on six ECCO conferences, and before she left FECS, set up the core programme for the seventh in Barcelona in September 2007. Although sometimes overshadowed by the prestigious American ASCO conference, ECCO flourished and attendances doubled.

"ECCO is still the cathedral of oncological conferences in Europe. It is the unique platform for multidisciplinary collaboration in oncology in Europe. It is prestigious if you are invited to speak, and should be seen as an acknowledgement and stimulus for the increasing efforts in research in Europe. The only factor working against conferences of that size is the growing tendency for people to focus on conferences in their specific area of research, very much the result of science and research becoming fragmented.

"One of the most important issues is that European research needs to be distributed in the first place amongst communities in Europe. Americans promote their own research. We should do that more."

The FECS conference unit also grew: at one time,

"Still the cathedral of oncological conferences in Europe". Vantongelen put together the core scientific programme for ECCO 14 before leaving FECS for new challenges

"ECCO is the unique platform for multi-disciplinary collaboration in oncology in Europe"

"The new generation of oncologists, who are not stuck in old politics, are the driving force of this future"

12 staff were organising meetings, symposiums and conferences across Europe. Vantongelen coordinated the first European Breast Cancer Conference (EBCC) in Florence in 1998, which put clinicians, scientists and advocates on the same platform and astonished the organisers by attracting 3,000 people.

The other event of which she is most proud is the annual Flims (Switzerland) Workshop on Methods in Clinical Cancer Research for young researchers, sponsored by FECS with the American Association for Cancer Research (AACR) and ASCO.

Oncologist Jean-Pierre Armand took Vantongelen to visit the Vail Clinical Trial Workshop in the US. He was determined to start something similar for Europe, and commissioned Vantongelen to make it happen.

"This was a fantastic idea. A young researcher comes with a study proposal and, during the workshop, is guided towards a feasible design addressing a sound scientific question. With the help of top experts in the field and individual counselling, they go home in five days with the finished protocol written. They work day and night, but when they go home on the Friday morning you can see great relief and victory in their eyes."

Over the eight Flims workshops with which she was associated, 95% of the researchers went home with a completed protocol, and half were approved by local ethical committees.

The Flims Alumni Club contains many future leaders in oncology, and an increasing number of previous Flims fellows now present research at ASCO and at ECCO.

Vantongelen left FECS in 2006. She will not discuss her departure, but it was clearly an unhappy time in her professional life.

Return to research

She arrived at BIG last November, delighted to be back with clinical research, but characteristically, with some self-doubt. "I was a bit frightened that I missed too many important translational research developments and the legal- and regulatory-related issues that I absolutely need here. I caught up reasonably rapidly, but still there are so many things to learn, specifically about the new complex trials we run and plan for the future."

BIG's aim is to facilitate the conduct of large and difficult breast cancer clinical trials and to reduce wasteful duplication. Vantongelen arrived as BIG was about to launch the ALTTO and Neo-ALTTO trials, evaluating lapatinib, a small tyrosine kinase molecule, given either adjuvant or neo-adjuvant, alone, sequentially or in combination to trastuzumab (Herceptin) for patients with HER2-positive, early-stage breast cancer. The ALTTO trial is jointly conducted with the US North Central Cancer Treatment Group and BIG is coordinating the activities between research groups in Europe, Japan, Taiwan, Australia, New Zealand, South Africa, and in North and South America, altogether representing over 1,200 institutions. ALTTO is indeed the first truly global adjuvant trial for breast cancer.

Vantongelen has seen clinical research in oncology develop from the early prospective clinical trials to the complex modern global trials with the fascinating translational research opportunities of today.

"I'm a believer. I believe in the future of oncology in Europe; there are many challenges, but there are also many good and enthusiastic people around. Times are changing and research is moving faster than ever before – so are people and opportunities, and the new generation of oncologists, who are not stuck in old politics, are the driving force of this future."

As her 60th birthday approaches, Vantongelen looks forward to spending more time with her grandchildren and husband. She recalls the time when her three children were under the age of seven as a period of complete exhaustion that went by in a blur.

"I was studying. I was working. I was raising children, Suddenly, you realise that they are teenagers. Now with the grandchildren you get a second chance, but you never get a third one! I enjoy every minute of it and, while I don't have too many spare minutes right now, I want to make firm plans for that."

New breast care network seeks to push up standards across the globe

➜ Jim Boumelha

Cancer clinicians have a long history of collaborating across national boundaries to try to find out which therapies and protocols are most effective. Now a group of leading breast clinics have scored a first by setting up an international network focused primarily on improving the quality of their own clinical practice.

The breast cancer community prides itself in blazing a trail for other parts of oncology to follow, and this year it looks like it has done it again, with the establishment of the first international network of specialist clinics.

The SenoNetwork builds on work done by Europe's professional mastology organisation EUSOMA, together with the patient advocacy group EUROPA DONNA, to promote specialist breast units as the best environment for diagnosing and treating breast cancers.

It aims to help patients locate breast units in their country where they can receive high-quality treatment or get a second opinion. A directory published on their website www.senonetwork.org gives the contact details for all the members of the Network, together with 'key facts' about how many dedicated breast surgeons work there, what services are provided and the number of new patients treated and mammograms done every year.

More importantly, perhaps, for the professionals involved, it aims to push standards of treatment up further.

Still in its infancy, the SenoNetwork has already attracted 38 breast units across the world – all but four, at this stage, based in Europe. Jacques Bernier, head of radiation oncology at the Genolier Swiss Medical Network and president of the SenoNetwork's scientific committee, believes its strong vision will form the bedrock for steady growth. "Our mission is threefold: to develop synergies among the breast units and to have good communications between groups; to help the physicians and the nurses of member institutions improve their work, through exchange of information; and to help cancer patients find the right place for expert treatment and information," he said.

Signing up to that mission statement is, however, not enough to guarantee membership. Clinics wishing to join the SenoNetwork and be listed in their directory are required to submit detailed information about staffing, the functional and structural environment, equipment, case loads, training and quality assurance, based on the minimum requirements for a breast unit drawn up by EUSOMA and recommended by the European Commission. "The goal is not to fix very rigid rules," says Bernier, who notes that building international organisations requires taking into account the diversity in medical culture and traditions as well social environment and resources. "It is to see that, in terms of infrastructure, resources and a multidisciplinary approach, the centre is acceptable in such a network."

Different environments

The private Hisar Intercontinental Hospital in Istanbul, Turkey – currently the only member of the Network in Asia – can certainly compare with most of its European counterparts.

It has state of the art equipment, provides reconstructive surgery, professional counselling and rehabilitation services, and is very strong on breast conservation and the use of sentinel node biopsies – its clinical director Serife Simke trained with Umberto Veronesi, who was a pioneer in these procedures.

However, it operates in a very different environment from many breast units in Europe, and Simke believes her clinic has an important role spreading knowledge to other centres treating breast cancer in Turkey.

"In some instances doctors do not recommend conservation surgery because they think that the patient cannot reach the radiotherapy or chemotherapy centre after surgery. Sometimes the problem is that they simply don't know how to do it. We try to share our experience with other institutes. We have a national congress on breast cancer surgery, and we also have local meetings, twice a month, where we get together with other colleagues who are doing breast cancer surgery."

It is the educational possibilities – not least the chance to participate in clinical trials – that particularly attracted Simke to joining the SenoNetwork. "I believe that one of the best solutions to get knowledge is to enter in a trial and to share the findings in my country. We have a lot of problems in breast cancer surgery, and we have no institute that specialises in breast cancer in Turkey. We need immediately to enter trials and to get some real statistics about these problems."

Quality care is a team effort. All breast units in the SenoNetwork work as teams of specialists from a variety of disciplines, including radiologists, pathologists, surgeons, medical oncologists, specialist breast nurses and more. The department of breast cancer at the European Institute of Oncology, pictured above, is one of seven Italian breast units listed in the SenoNetwork directory

The challenges facing the CHU Henri Mondor, one of France's leading teaching hospitals in Créteil near Paris, are very different. But here too, the greatest asset of membership in the SenoNetwork is seen as the potential it offers for participating in research. Jean-Leon Lagrange, head of the radiotherapy department at the hospital's breast unit, refers to recent French studies that show outcomes are better where patients are treated according to a trial protocol. "So it's probably true to say that patients are treated best where the physician is involved in research or in group of research. SenoNetwork is one of the groups – it is also an international group."

As a radiation oncologist he is looking forward to new proposals for translational research protocols – part clinical activity and part laboratory research – "because, in my view it's time to obtain biological data and to match it with the clinical data and the results of the prospective protocols, to obtain the best results of treatment." He identifies as a particular priority finding ways to identify which patients require no adjuvant therapy – attention is currently focused on two alternative molecular signatures. "I think it's a very important question for two reasons: first because there is toxicity in adjuvant therapy, and second for economic reasons."

Simke believes her clinic can help spread knowledge to other centres treating breast cancer in Turkey

Promoting best practice

Lagrange also looks beyond his own hospital to what the SenoNetwork can offer to countries where cancer treatment, and breast cancer care in particular, is less developed. "I have a long experience in visiting Chinese and Libyan hospitals and I've done many conferences there. One important message we need to get over is that you cannot have high standards of treatment if there are no meetings or conferences where you can plan the treatment strategy for each new patient. When I discuss with my Chinese residents they say, 'It's the surgeon who sees the patient first and he advocates mastectomy,' and every woman is treated with mastectomy, even though we know that in certain conditions this is not a good solution." He believes one of the most important things the SenoNetwork can do will be to help spread the practice of holding multidisciplinary boards among practitioners working in breast cancer across the world.

Bernier agrees that changing clinical practice must lie at the heart of the work of the SenoNetwork, but emphasises that even where multidisciplinary teams are functioning well, teams have a lot to learn from one another. New knowledge is also being generated all that time, which needs to be incorporated into the way the teams work. "We are dealing with complicated things in terms of the lab and clinical research. What we want to do is to translate any recommendation on diagnosis or therapy into a user-friendly resource… and then circulate the kind of information that would enable every professional in each centre to choose the right decision process for a given situation."

This is all very much work in progress. The advisory board of the Network's scientific committee met for the first time in Barcelona last month to try to hammer out strategic options. There is a need to define the type of information that centres should be looking to circulate within the Network, says Bernier. "For instance it's very important that when you get an important result from a clinical trial that the information in these results is spread out among the member institutions."

He also envisages a role for the scientific committee in evaluating innovative therapies, such as partial breast irradiation and intra-operative irradiation. Then there is the question of developing some consensus guidelines for diagnosis and treatment. "The role of the scientific committee is certainly to develop that kind of consensus guideline and to have a strategic view on the platform in terms of exchange of information to help doctors, and to help nurses improve the quality of their work."

This would be an ambitious agenda even if it were confined to Europe. It is all the more so, given the international aspirations of the SenoNetwork "It won't be easy," Bernier admits. "Sometimes you will have to create several levels of recommendations in the guidelines, according to the level of expertise of the centre – a minimum package or an extra package – so it's a very long process. They key thing for us is to encourage among breast clinics who are members of the SenoNetwork a real dedication to all forms of clinical management, improving the quality and effectiveness of breast cancer care."

Talking quality. Representatives from 19 of the 38 members of the SenoNetwork met for the first time in Barcelona in September to discuss how the Network can best help them improve the care they provide. They came from Belgium, Brazil, the Czech Republic, Hungary, Italy, Slovenia, Sweden, Switzerland, Turkey and the UK. Jacques Bernier is pictured standing

The directory. At www.senonetwork.org patients can find a list of quality breast clinics in their own country. Data on staffing, patient numbers and services offered, are provided for each clinic, together with contact details

Changing clinical practice must lie at the heart of the work of the SenoNetwork

The X factor

What is the secret behind a high-performance cancer system?

Anna Wagstaff

How can cancer services deliver top-quality, affordable care to aging populations in an era of fast-changing treatments and escalating costs? Five countries with something to offer and something to learn met to compare notes.

Would you rather be treated for cancer in the US, which spends 17% of gross domestic product on healthcare, or in Canada (10% of GDP), Germany (11%), France (10%) or the UK (8.5%)?

That is the question answered at an informal meeting in London in June , by a roomful of people set on improving cancer services in these five countries.

Votes were widely distributed, with France topping the poll by a small margin. The US – the only country that can boast an average waiting time of six hours from a positive breast scan to excision – came further down the list.

Each system has its strengths and its weaknesses. If accessing latest treatments and techniques was the priority, the US had to be the system of choice, with France the leading contender in Europe. For those who valued most the right to choose where to be treated – the US, France and Germany scored highly, though none offer patients enough information to make an informed choice. If quality control and transparency comes first, Canada would be a good choice, with a strong infrastructure for reporting and analysing key quality data. Germany scores well if you look primarily at centres of excellence. If you look for consistency in standards and performance across the system, then the UK, with cancer networks built around minimum volumes and specialist multidisciplinary teams, would be a good bet.

Waiting times, integration between different parts of the care system and expense will also have influenced the poll. Those who voted for the US will have assumed they were not one of the 45 million who have no health insurance.

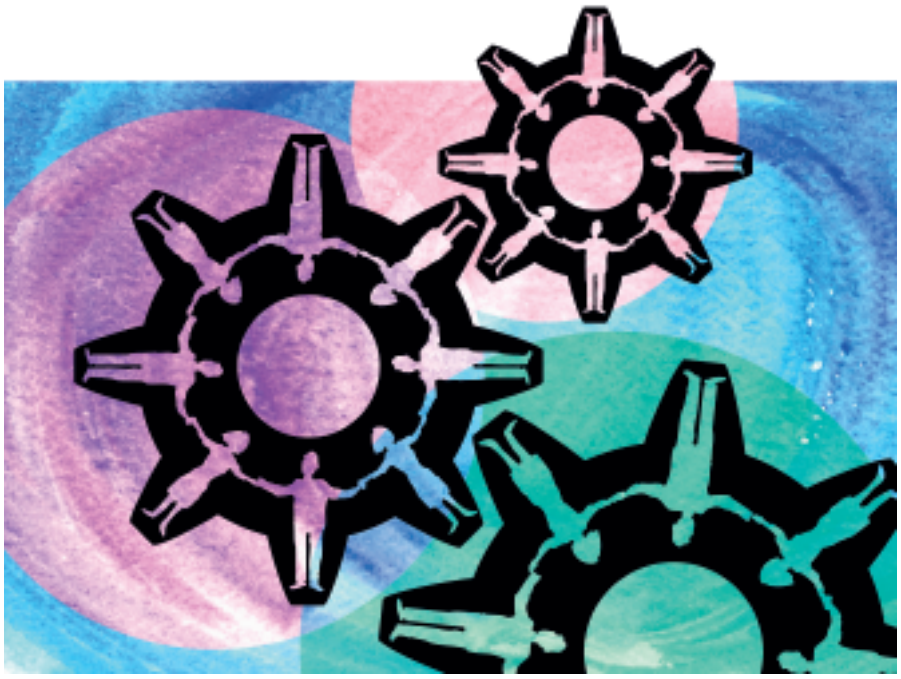
The five systems

These five cancer systems have all recognised that aspects of their systems need improving. Each is trying to find ways to deliver top-quality, affordable care to aging populations at a time when treatments are changing fast and the cost of new therapies is escalating.

The five systems vary widely in culture, organisation and funding mechanisms. At one end of the spectrum, the UK has a publicly provided health system and a 'top down' command and control approach. This meant that when Prime Minister Tony Blair made a commitment to improve Britain's cancer care, it was possible to move quite quickly to a system in which all patients are referred to specialist centres where care is planned by 1,400 multidisciplinary teams (MDTs), each with a minimum volume of patients and working to standardised practice guidelines. Not for nothing is the UK's national cancer director dubbed the 'Cancer Tzar'.

But the Tzar himself, Mike Richards, told the meeting that the top down approach has limitations. It can push through change, but it is less effective at reducing waiting times, or at ensuring 100% attendance at MDT meetings, adherence to guidelines or a grass-roots culture of monitoring and improvement. The UK's principal interest was to find ways to enhance the performance of its restructured system.

Responsibility for ensuring cost-effectiveness in the UK lies with the National Institute for Health and Clinical Excel-



GETTY IMAGES

lence (NICE), which makes recommendations on whether new therapies offer sufficient additional benefit to justify reimbursement, and also lays down practice guidelines.

In the US, by contrast, healthcare is seen as a consumer good, and the role of the state is limited largely to promoting competition in a system driven by consumer choice. It is quick to embrace new therapies; in some areas (like that six-hour wait time) it out-performs anything in Europe, and many of its 61 comprehensive cancer centres are world class. These centres, however, treat fewer than one in ten American cancer patients. Nine in ten are treated in a wide variety of settings, with a relatively low adherence to guidelines, mimimal feedback on quality, and varying outcomes.

The big issue for the US is cost-effectiveness. Because healthcare is not socially funded, there are no constraints on spending other than the ability to afford insurance. Consumer choice is not effective at pushing up standards, because there is no authority responsible for collecting quality data. Surgeons, paid on a fee-per-service basis, have an incentive to opt for surgery, radiotherapists have an incentive to break therapies into short sessions – up to five times more than the evidence warrants. Medical oncologists make around 50% of their income in profit mark-up from the drugs they 'retail' to their patients. There is a high level of off-label use – an investigation by the largest health insurer revealed that 12% of patients given Herceptin (trastuzumab) had never been given a HER2+ test, or had tested negative.

In the absence of any federal agency responsible for driving up standards, the American Society of Clinical Oncology is promoting a system of voluntary self-reporting. Clinics joining the Quality Oncology Practice Initiative (QOPI) are required to select a sample of cases from the previous six months, and report on a variety of measures, including adequacy of documentation, chemotherapy planning and pain control, with other measures specific to the type of cancer. QOPI enables clinics to assess their performance, compare themselves with other practices, identify shortcomings and monitor improvements. It was rolled out nationally in March 2006, with an enthusiastic early take up. However, getting beyond 10% of practices may require incentives, possibly by health insurance companies, and external validation.

With spending on cancer rising at 13% a year, medical insurance premiums rising at 9%, incomes rising at 3% and almost one in five Americans unable to afford health insurance, one key thing the Americans were looking for from this meeting was a way to impose rational constraints.

The Canadian, French and German systems lie between these two extremes. The Canadian system was described as "like the UK but Federal" – hospital-based care is provided by a public health service, largely funded by taxation, and the system operates under tight spending constraints.

Cancer care hit the political agenda in the early part of this decade when lengthening waiting lists led to a steady flow of patients crossing the border to pay for treatment in the US, sparking a crisis of confidence. Bill Evans described how Cancer Care Ontario focused on developing a system for gathering data on key quality indicators, which were used to provide feedback to hospitals and clinicians, and to monitor improvements. It aimed to introduce transparency into the system with a view to rebuilding public

Surgeons paid on a fee-per-service basis have an incentive to opt for surgery

KEY COMPONENTS OF A HIGH-PERFORMANCE SYSTEM

- A strong political will to overcome resistance to structural changes and cost-effectiveness measures
- Engaging clinicians in the development and implementation of guidelines, and 'self-assessment' schemes like QOPI
- Ensuring that every patient has care planned at a multidisciplinary meeting – with investment in infrastructure, such as videoconferencing
- Encouraging a strong patient voice to promote services geared to patients priorities, such as transparency and a smooth passage between different parts of the care system
- Collecting good data on performance indicators – including staging and diagnosis, adherence to guidelines, pain and symptom management – to inform clinicians and give patients informed choice
- Aligning incentives with key quality objectives. Paying according to key performance indicators is one way; promoting competition on the basis of informed patient choice is another
- Avoiding adverse incentives, such as fee per procedure. Imposing minimum volumes can also provide an incentive to overtreat. (Having to justify an intervention at a multidisciplinary hearing can be an effective counterbalance)
- Developing IT systems capable of sharing information, scheduling and tracking patients throughout their cancer journey

confidence and encouraging patients to play a role in getting the best from their service. Though still limited in scope, the data published on their website www.cancercare.on.ca/qualityindex2007/ is thorough and user-friendly.

"We want a greater degree of openness by providing information on current best practices and engaging patients in making good decisions for themselves," said Evans. "It is also good to raise public awareness of the performance of the healthcare system. It puts everyone on notice of where we are and where we need to make improvements."

With a system based largely on salaries rather than fee-per-service, adherence to guidelines is strong. A robust approach to evaluating the cost-effectiveness of new therapies and devices helps restrain spending. For instance, Ontario does not reimburse for Avastin (bevacizumab), and is even considering whether PET scans add sufficient value to justify the cost.

The French and German systems are closer to that of the US, in that both are relatively fragmented with a strong element of private provision (which came as a surprise to the US contingent). There are, however, important differences. In France and Germany, healthcare is seen as a social responsibility, and most of the funding comes either from state run or social (non-profit) insurance schemes. Dealing with the rising cost of cancer care by offering worse treatment for those less able to pay is not publicly acceptable.

Germany recently set up a federal body for evaluating new therapies, called IQWiG (Institut für Qualität und Wirtschaftlichkeit), which caused ructions amongst clinicians. However, the trend towards greater scrutiny of the cost-effectiveness of new treatments seems likely to continue.

France prides itself in promoting cost-effectiveness by focusing on effectiveness, paying a premium for truly innovative drugs and encouraging research to find out how to use available therapies to greatest effect. The PHARE trial, looking at whether Herceptin is equally effective used adjuvantly for six months as for a year could save the health budget millions.

Scepticism about state intervention in civic life, so strong in US culture, is not reflected in France or Germany, giving scope for governments to take a lead. When French President Jacques Chirac made cancer one of his presidential themes, he helped to push through comprehensive legislation giving patients a right to information, psychosocial support and even access to mortgages. A national cancer institute, INCa, was given dual responsibility for clinical quality and safety as well as clinical research. Regional cancer networks must ensure that every cancer patient's care is planned at a multidisciplinary board, regardless of where care is delivered. Rules on minimum volumes have been introduced, though these are currently set quite low.

French cancer networks provide an example of how far it is possible to restructure a cancer service in which care provision remains fragmented, being spread between 20 comprehensive cancer centres, a sprinkling of university hospitals, and around 700 public district hospitals and 1,500 private clinics, with almost 50% of surgery done by the private sector.

In Germany, cancer has not become a political priority, which may indicate a lack of major problems – or a lack of data on what is happening beyond the prestigious university hospitals.

A mark of quality. QOPI is a system of voluntary self-reporting being promoted by ASCO to help US clinics improve their own performance

Getting everything right is a complex business requiring a range of different pressures and incentives

Professional bodies have promoted systems of accreditation as a way of pointing patients towards better care, and as an incentive for clinics to fulfil minimum quality criteria. But accreditation is not mandatory, and the system is confusing because so many bodies run accreditation schemes.

Recent reforms have tried to improve efficiency by tackling the separation of hospital and ambulatory care sectors – reducing duplication of tests, improving communication, ensuring treatments are carried out in the most suitable, cost-effective settings, and improving the patient experience. Legislative changes have made it possible for cancer services to be provided within 'centres for integrated oncology' (CIOs), incorporating providers from all parts of the patient's care from diagnostics through therapy and aftercare – whether that be hospice care or rehabilitation. Having a single structure makes it easier to develop joint guidelines and shared information systems. Because the CIO also incorporates payers, the system allows insurers to make a single payment, based on stage of the disease, to cover all the costs of treatment, leaving it up to the practitioners to decide precisely how to distribute the funds.

A separate initiative on disease management programmes introduced regulations for care targets, drugs, quality management and documentation for a number of diseases, although breast cancer is the only cancer currently included. Early data indicate an improvement in the quality of care, but there is resistance from some clinicians, who find it limits their therapeutic options and fear it will slow the introduction of new treatments. There are some financial incentives for setting up CIOs and working within a disease management programme, but neither is compulsory. It is up to clinicians and health service managers to drive change, institution by institution. This means that, where they are adopted, staff are likely to be committed to making them work. The downside is that patients treated at clinics with no great tradition of innovation and quality monitoring are unlikely to benefit.

The importance of finding out what is happening across cancer care in the country, as a precondition to pulling up standards, was a message the German delegation found particularly helpful.

In fact, everyone took something useful home from the meeting.

- For the **Americans**, the key issue was the need to ratchet down expectations and use comparative effectiveness data to reduce costs. "Whether we can import that into the US because of cultural differences is still the open question," said Eric Schneider of the Harvard School of Public Health.
- For Franz Kohlhuber, head of project funding at **German** Cancer Aid, the key message was the importance of reliable data. "When you see data from other countries – and how it is used – it becomes obvious how badly it is needed. Maybe we have to spend money on this first."
- For the **UK**, it was a question of stimulating improvements by moving from data about process to data about outcomes. "Most of our data are structure data: 'Do MDTs meet, do they follow guidelines…?' We would like output data as well, the sort of quality index data the Canadians are gathering. Data for embarrassment and choice is the key," said the national cancer director, Mike Richards.
- Helping foster a grassroots culture of monitoring and improving quality was a concern for the **Canadians**. "We are probably guilty at times of pushing too many things down on to the practitioners in the community. But we need to engage them in guideline development and in the decision making for changes in how care is delivered and so on," said Evans of Cancer Care Ontario.
- Laurent Borella, from the **French** INCa, was also looking for a greater variety of incentives, financial, political and patient pressure. "Maybe we have to work on both sides of the problem. Public and legal schemes like Britain and France; but also data on efficiency and outcomes to moderate the payments system for hospitals depending on their outcomes."

The different experiences of the five countries shows that getting everything right is a complex business, requiring a range of different pressures and incentives. "We can no longer focus only on conventional surveillance indicators of performance," said Terry Sullivan, CEO of Cancer Care Ontario and convenor of the five country meeting. "It seems clear from this exchange of views that three broad levers are essential: good use of performance measurement, reporting and incentives; real engagement of key practice leaders and patient groups; and alignment of institutional, political and clinical leadership. Countries can learn a lot from one another."

The meeting was financed by a grant from the Commonwealth Fund. A symposium looking at these issues and drawing on the London meeting will be hosted by the European School of Oncology at the World Cancer Conference, Geneva, in 2008.

NEWSROUND

Selected reports edited by Hannah Brown

Patients 'should welcome' rash from EGFR inhibitors

→ Clinical Cancer Research

Development of an itchy pustular rash over the torso, head and face of patients treated with inhibitors of the epidermal growth factor receptor (EGFR) – a type of targeted drug that is increasingly used to treat several types of cancer – may actually indicate the treatment is working well, according to a recently published analysis of two phase III trials. According to the study, the worse the rash is the more likely patients are to survive their cancers or at least maintain good control of the disease. Researchers from OSI Pharmaceuticals, the company that manufactures the EGFR inhibitor erlotinib (Tarceva), analysed side-effect data and outcomes from two phase III studies that showed a positive result after treatment with their drug, which is just one of many similar agents currently being prescribed by oncologists.

Both trials from which the researchers drew their data had made a special note of a rash among patients who had received the drug and those who had not – and it is this information the researchers used to asses a link between severity of the rash and effectiveness of the treatment. The first trial compared treatment with 150 mg erlotinib daily with placebo in 731 patients with stage IIIB/IV non-small-cell lung cancer who had failed at least one prior chemotherapy regimen. Overall survival, tumour response, progression-free survival, and time to symptom deterioration were all improved in the group taking erlotinib. The second study evaluated erlotinib plus gemcitabine compared with placebo plus gemcitabine for the treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer. Erlotinib again improved survival. Most of the patients taking erlotinib in both studies developed a post-treatment rash, which was graded for severity by the clinical trial teams. The OSI investigators excluded from their analysis all patients who had died within 28 days of therapy, because they reasoned that this time frame was not sufficient for a rash associated with outcome to have developed. This specific cut-off was chosen because there was a large difference in the incidence of rash among those who died within four weeks and those who survived longer (<20% vs >70%).

In the first study, 81% of the 444 erlotinib-treated patients experienced a rash. Patients who developed grade 1 rash survived 144% longer than patients who did not develop rash, and patients with grade 2 rash survived 245% longer than patients who did not develop rash. In the other study, among the 254 patients in the erlotinib plus gemcitabine group the incidence of rash was 71%. But in the second study the incidence of rash among the placebo group was, at 30%, almost double that in the first trial. As a result, there were no statistically significant differences in outcomes between the patients with rash and those without. The authors explain the discrepancy between the two studies by explaining that their analysis of the correlation of rash with outcomes in the second study was potentially confounded because rash is an adverse event associated with both erlotinib and gemcitabine treatment.

Concluding that "the patient who does not develop a characteristic rash within 2 to 4 weeks is less likely to benefit from erlotinib," the researchers note that physicians and patients should view the development of rash as a desirable outcome – perhaps as a sign of erlotinib-induced biological effect. They emphasise the need to develop methods for managing the rash without interfering with the improvement in outcomes it brings. "Optimal management of rash in patients on EGFR inhibitors remains somewhat controversial, but aggressive treatment of the side-effects may allow patients to continue receiving therapy without dose interruption or drug discontinuation," they write. As part of the clinical management of this side-effect, patients should also be counselled to help them regard the development of the rash as a positive step, the researchers suggest.

■ Correlation between Development of rash and efficacy in patients treated with the epidermal growth factor receptor tyrosine kinase inhibitor erlotinib in two large phase III studies. B Wacker, T Nagrani et al. *Clin Cancer Res* 1 July 2007, 13: 3913–3921

More evidence for the surgical learning curve

→ JNCI

Patients with prostate cancer who are operated on by surgeons who have done more than 250 radical prostatectomies – an operation involving complete removal of the prostate gland – are much more likely to avoid recurrence of disease than those operated on by less experienced surgeons, according to a study published in the *Journal of the National Cancer Institute*.

Researchers from the Memorial Sloan-Kettering Cancer Center in New York analysed outcome data from 7,765 patients who had radical prostatectomies done by 72 surgeons at four institutions between 1987 and 2003. The researchers quantified the surgeons' experience by the number of times they had performed the procedure before each operation, and adjusted for case mix to assess the effect of surgical technique and skill on outcomes.

The patients were assigned to one of five groups according to the experience of their surgeon at the time of their operation: <50, 50–99, 100–249, 250–999, or ≥1000 prior radical prostatectomies. Follow-up consisted of measuring serum levels of prostate specific antigen (PSA) every 3–4 months during the first year after surgery, and less frequently in subsequent years. Cancer recurrence was defined as a serum PSA of more than 0.4 ng/ml followed by a subsequent higher PSA level.

More surgical experience was associated with a greater likelihood that the patient's cancer would not return after their operation. The learning curve for this procedure was very steep; there was dramatic improvement in patient outcomes as surgeons' experience increased up to 250 operations, after which increasing experience had little influence on cancer recurrence. Patients treated by inexperienced surgeons (for example, those with 10 prior operations) were nearly 70% more likely to have evidence of recurrence of their prostate cancer within five years than those whose surgeons had performed 250 operations.

"Our findings also have implications for education in surgical oncology," say the authors. "Although the successful practice of surgery necessarily presumes a lifetime of learning, the large number of cases required before the learning curve plateaus suggests the need to expand opportunities for training in surgical technique for surgeons in the early years after residency training."

■ The Surgical learning curve for prostate cancer control after radical prostatectomy. AJ Vickers, FJ Bianco, AM Serio et al. *J Natl Cancer Inst* 1 August 2007, 99:1171–1177

High-dose chemotherapy for refractory testicular cancer

→ New England Journal of Medicine

Patients with advanced testicular cancers whose disease has progressed despite receiving standard chemotherapy can be cured by additional drug therapy at very high doses, according to a recently published retrospective case series.

The vast majority of men who develop testicular cancer are cured of their disease by the standard chemotherapy regimen, which involves multiple courses of cisplatin. However, for the small proportion who do not respond to this treatment, other options must be sought. For most patients, these options include salvage chemotherapy with cisplatin plus ifosfamide plus vinblastine or paclitaxel for four courses, or high-dose chemotherapy with autologous haematopoietic stem-cell transplantation to rescue the bone marrow from the myeloablative effects of chemotherapy.

Reporting a series of patients who were treated at Indiana University, Lawrence Einhorn and colleagues recalled 10 years' experience with the latter option. Between February 1996 and December 2004, 184 patients were treated with carboplatin chemotherapy at five times the dosage administered to men receiving initial therapy, followed by peripheral-blood stem-cell rescue.

During a median follow-up of 48 months, 116 of the patients (63%) were continuously disease free. Of these 116 patients, 104 (90%) were disease-free for more than two years. Six additional patients had complete remission of disease, four after receiving paclitaxel plus gemcitabine and two after undergoing subsequent resection of a germ-cell tumour. The toxic effects of high-dose chemotherapy were primarily myelosuppression, mucositis, nausea, vomiting, dehydration, peripheral neuropathy and hearing abnormalities. There were three sudden drug-related deaths; two were due to hepatic failure, and one was due to pulmonary toxic effects.

The authors conclude that, "There should be little or no debate on the use of high-dose chemotherapy for a patient with a germ-cell tumor that is refractory to platinum-based chemotherapy or that is not cured by a cisplatin–ifosfamide regimen as salvage chemotherapy. In our study, 18 of 40 patients with progressive metastatic disease and tumors that were refractory to platinum remained disease-free for a median of 49 months (range, 22 to 110), and 22 of 49 patients who received high-dose chemotherapy as third-line or later therapy remained disease-free for a median of 46 months (range, 25 to 112)."

■ High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. LH Einhorn, SD Williams, A Chamness et al. *New Engl J Med* 26 July 2007, 357: 340–348

FDA: tomato consumption does not decrease cancer risk

→ JNCI

There is only limited evidence for an association between eating tomatoes and a decreased risk of certain cancers, according to an article published in the *Journal of the National Cancer Institute*.

Several studies have reported an association between the consumption of tomatoes or

lycopene, an antioxidant that gives tomatoes their red colour, and a decreased risk of some cancers, particularly prostate cancer. But before foods and dietary supplements can be sold in the US with such claims on their packaging, the US Food and Drug Administration (FDA) must review and approve these claims based on the available scientific evidence.

Reviewing their deliberations about the anti-cancer properties of tomatoes and lycopene, FDA panel member Claudine Kavanaugh and colleagues found no evidence that tomatoes reduced the risk of lung, colorectal, breast, cervical or endometrial cancer. However, there was very limited evidence for associations between tomato consumption and reduced risk of prostate, ovarian, gastric and pancreatic cancers. Based on this assessment, the FDA decided to allow qualified health claims for a very limited association between tomatoes and these four cancers. Their analysis found no credible evidence that lycopene, either in food or in a dietary supplement, was associated with reduced risk of any of the cancers evaluated. For prostate cancer, for example, the FDA issued this statement: "Very limited and preliminary scientific research suggests that eating one-half to one cup of tomatoes and/or tomato sauce a week may reduce the risk of prostate cancer. [The] FDA concludes that there is little scientific evidence supporting this claim."

In an accompanying editorial, Paul Coates, of the National Institutes of Health, says the limited number of clinical trials available made the FDA's decision a hard one. "However," he says this lack of data does not diminish "the importance of using evidence-based review principles to evaluate important diet–health relationships." He added, "It may be argued that evaluating a diet–health relationship is precisely the circumstance in which systematic review techniques can be most appropriate and effective, because they are transparent and objective, and the search and review strategies could be exactly reproduced by others."

■ The U.S. Food and Drug Administration's evidence-based review for qualified health claims: tomatoes, lycopene, and cancer. CJ Kavanaugh, PR Trumbo, KC Ellwood. *J Natl Cancer Inst* 18 July 2007, 99:1074–1085

■ Evidence-based reviews in support of health policy decisions (editorial). PM Coates. ibid p 1059

Taking lapatinib with food could increase effective dose and save money

➔ Journal of Clinical Oncology

Encouraging patients to ignore prescribing advice and take the targeted drug lapatinib with food could increase the effective dose by five times, thereby reducing the cost of treatment, argue Mark Ratain and Ezra Cohen from the University of Chicago in the *Journal of Clinical Oncology*. They add, however, that studies of this suggestion are needed before it should be considered standard practice.

Current prescribing notes for lapatinib, a drug that inhibits both the epidermal growth factor receptor and another tyrosine kinase called ERBB2, say patients should take the tablet at least an hour before food or wait until an hour afterwards – because those were the conditions under which the drug was tested, and they form the basis of its approval for market. However, Ratain and Cohen claim that pharmacokinetic data on the bioavailability of lapatinib show that food significantly increases the concentration of the drug in the body. What is more, if the meal is high in fat, the concentration of the drug is further increased. As a result, 500 mg of lapatinib taken with food may be as effective as taking the currently approved 1,250 mg without food.

Lapatinib was approved by the FDA in March of this year for women with advanced HER2-positive breast cancer. The FDA approved the 1,250 mg dose of lapatinib based on a large phase III clinical trial demonstrating its effectiveness and safety at that dose without food. The dose is taken as five 250 mg tablets on an empty stomach, and costs $2,900 (€2,050) per month. However, applying Ratain and Cohen's rationale could lead to cost savings of 60% or $1,740 (€1,250). "As we enter an era of 'targeted' anticancer agents, with a monthly cost measured in the thousands of dollars, we should view drug–drug or drug–food interactions as opportunities to lower costs," they write. However, the authors strongly emphasise that a formal pharmacokinetic study of a lower dose of lapatinib with food would be needed to confirm these findings before any change in dosage could be considered safe and effective.

■ The value meal: how to save $1700 per month or more on lapatinib.MJ Ratain, EE Cohen. *J Clin Oncol* 10 August 2007, 25:3397–3398

Lymphoedema is inversely associated with node status

➔ Annals of Surgery

Lymphoedema following surgery or radiotherapy for breast cancer may be determined by factors that pre-date the treatment, according to a recent study.

Breast-cancer related lymphoedema – swelling of the arm accompanied by feelings of discomfort and heaviness – occurs in women who are treated with surgery or radiotherapy to the lymph nodes under the arm, although only some women suffer from the condition. The cause is poorly understood, but it is generally assumed that treatment in some way impairs lymphatic drainage and by doing so causes the arm to swell. In this study, researchers pooled data from two studies looking at the relationship between axillary lymph-node dissection and lymphoedema. In all, data on 212 patients who had undergone surgery to their underarm lymph nodes, but no radiotherapy to this area, were analysed. Assessments of the extent of arm swelling were done by taking the circumference of the arm at 4 cm intervals from the wrist and, from those measurements, an estimate of arm volume was calculated. Measurements were taken both pre- and postoperatively at several pre-specified time points. Average arm volume changes were then compared between patients with positive nodes and those with no evidence

of tumour spread. The researchers also investigated trends in arm volume changes according to the number of positive nodes.

Positive node status (i.e., evidence of tumour in one or more of the dissected lymph nodes) was significantly associated with swelling in the lower arm in study 1 and for both studies combined. Adjusted for tumour size, time since operation, and repeated measures, arm volume excess was reduced with increasing numbers of positive nodes, a finding that was significant in study 1 and in both studies combined.

Although a number of previous studies have suggested a relationship between lymph-node positivity and lymphoedema, many of them are affected by the confounding effect of axilliary radiotherapy on lymphoedema. This study addressed that problem. The results are counterintuitive to current understanding of the pathophysiology of lymphoedema, which implies surgery and/or radiotherapy are the cause, say the authors. "Our results suggest that while these treatments bring on the condition, its severity or extent is determined by other factors that predate the therapy," they conclude.

■ Lymph node status and breast cancer-related lymphedema. AD Purushotham, TM Bennett Britton, MB Klevesath. *Ann Surg* July 2007, 246:42–45

Xerostomia must be prevented to improve quality of life

➔ Int J Radiat Oncol Biol Phys

Detrimental effects of the common radiation-induced side effect of xerostomia – dryness of the mouth caused by damage to the salivary glands – increase over time and severely impact on the quality of life for patients with head and neck cancer, according to a recent study.

Xerostomia is the most frequently reported late side-effect of radiotherapy. Late side effects are generally considered irreversible and progressive and are, therefore, of substantial importance in determining patients' quality of life. But information about the clinical relevance of radiation-induced toxicity in terms of quality of life is scarce. Therefore, Dr Jellema and colleagues decided to investigate the impact of xerostomia on quality of life among head and neck cancer patients treated with primary radiotherapy.

Between December 1998 and January 2004, 288 patients with head and neck cancer were recruited to the study. All had a life expectancy of at least 12 months and all had received radiotherapy as a first-line treatment, with curative intent. Acute and late radiation-induced morbidity were assessed according to the Radiation Therapy Oncology Group criteria, first at six weeks, and then at six-monthly intervals. Patients were also assessed at these appointments using a cancer-specific quality-of-life questionnaire. Xerostomia was found to have a significant effect on different dimensions of quality of life, an effect that was more pronounced in female and younger patients. Moreover, the effect of xerostomia on overall quality-of-life outcome increases with elapsing time, even though the incidence of xerostomia decreases.

This is the first study investigating the impact of radiation-induced xerostomia on overall quality of life and, although some publications suggest that xerostomia may recover over time in some patients, it appears from these findings that for most the damage induced by radiation is permanent. These results, conclude the authors, underline the need to prevent the development of radiation-induced xerostomia.

■ Impact of radiation-induced xerostomia on quality of life after primary radiotherapy among patients with head and neck cancer. AP Jellema, BJ Slotman, P Doornaert. *Int J Radiat Oncol Biol Phys* 1 November 2007, 69:751–760

Exercise may improve adherence to adjuvant chemotherapy

➔ Journal of Clinical Oncology

Encouraging patients who are undergoing adjuvant chemotherapy for breast cancer to take either aerobic or resistance exercise might increase the chance that they will complete a full course of chemotherapy, according to the surprise findings of a recent study.

Adjuvant chemotherapy improves the chances of long-term survival, but also tends to cause fatigue and worsen physical functioning. The Canadian START trial – Supervised Trial of Aerobic versus Resistance Training – aimed to investigate whether exercise may improve the quality of life of patients on adjuvant chemotherapy. It examined the independent effects of aerobic and resistance exercise on quality of life, fatigue, psychosocial functioning, physical fitness, body composition and chemotherapy completion rates, along with side-effects.

The researchers recruited 242 patients with stage I–IIIA breast cancer who were just beginning their first-line adjuvant chemotherapy, and randomly assigned them to one of three groups: usual care (n=82), supervised resistance exercise (n=82) or supervised aerobic exercise (n=78). All completed a questionnaire, physical fitness test, and a bone mineral density scan at the time of enrolment.

The researchers found that neither resistance nor aerobic exercise significantly improved quality of life – something the researchers attributed, in part, to the wide variability in quality of life change scores among the patients on chemotherapy. But they observed that undertaking exercise seemed to contribute to improved self-esteem among trial participants and, surprisingly, to the chemotherapy completion rate.

Self-esteem was superior in both the exercise groups compared with usual care and the chemotherapy completion rate, as measured by relative dose intensity, was higher in both exercise groups: 78% and 74% of patients undertaking resistance and aerobic exercise, respectively, received 85% of their planned dose, compared with just 66% in the usual care group.

■ Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. KS Courneya, RJ Segal, JR Mackey, et al. *J Clin Oncol*, published online 4 September 2007, doi:10.1200/JCO.2006.08.2024