Cancerworld

Education & knowledge through people & facts

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Cora Sternberg

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Welcome to our World

Kathy Redmond ■ EDITOR

Welcome to *Cancer World* – the magazine for the European oncology community. *Cancer World* was formerly published as *Cancer Futures* – it has a new name and a new look, but its aim is the same: to help reduce the unacceptable number of deaths from cancer that are caused by late diagnosis and inadequate cancer care.

We know that our success in preventing and treating cancer depends on many factors. Tumour biology, the extent of available knowledge and the nature of care delivered all play a role. But equally important are the political, financial and bureaucratic decisions that affect how far and how fast innovative therapies and technologies are adopted into mainstream practice. *Cancer World* explores the complexity of cancer care from all these very different viewpoints, and offers you an insight into the myriad decisions that shape your professional world. We hope the magazine will become a lively forum for discussion and debate.

The strength of *Cancer World* lies not only in this broad approach, but also in its commitment to exploring issues through the lives and work of those in the field. We will give a voice to health professionals in all fields and at all levels, and offer a platform to those who are most affected by cancer – the people with the disease. We will include in-depth interviews with some of Europe's most influential oncology leaders, who will be invited to comment on breaking news, discuss complex and difficult issues and share their experiences in overcoming personal and professional challenges as they have pushed forwards the boundaries of their practice.

People with a high public profile also have an important impact on cancer care – they shape public attitudes towards cancer and influence how cancer services are delivered and research is conducted. In each issue of *Cancer World* we will feature an interview with a celebrity, politician or captain of industry who influences the field of cancer in some way. We hope that these stories will give our readers a broader perspective on cancer and perhaps inspire some initiatives that will help improve the care that cancer patients receive.

Oncology is a fast moving field, which places ever higher demands on us all, both professionally and personally. This is your magazine. It aims to support you in your job, by addressing the issues you tackle every day, and by giving you the information you need to do your job well. As Editor, I would welcome your comments and opinions on any of the diverse issues covered in the magazine, as well as suggestions on topics for inclusion in future issues.

All correspondence should be sent to the Editor at magazine@esoncology.org

Cora Sternberg: An American in Rome

Marc Beishon

When Cora Sternberg left the Memorial Sloan-Kettering in New York to make her way in Italy, she brought with her more than just expertise. From patient care to fundraising, the department of oncology which she heads at the San Camillo and Forlanini hospital complex in Rome now has a marked American flavour.

"When in Rome do as the Romans" is an old proverb that Dr Cora Sternberg, head of medical oncology at the city's sprawling San Camillo and Forlanini hospital complex, has distinctly mixed feelings about. A high-energy American by birth, she was smitten by the cultural attractions of Italy when she first came to live in Rome nearly 16 years ago. But, having already made her name as a top cancer researcher in the US, Sternberg has found the professional transition rather more of a challenge in terms of establishing a solid base for her primary goal – first rate clinical cancer care and research.

After working in several of Rome's hospitals and institutes, she became chief of medical oncology at the San Camillo and Forlanini hospital in 2002, and in a short time has transformed the department from a place carrying out only standard treatment to a clinical trials centre with a growing reputation. Patient care, too, has been upgraded greatly since her arrival, using a holistic model in which Sternberg firmly believes.

And from the start of her move to Italy, she was eagerly embraced by the European Organisation for the Research and Treatment of Cancer (EORTC), such that her involvement with research has hardly faltered. "At my very first EORTC meeting I was asked to take over bladder cancer research in Europe," says Sternberg. "I was surprised – but they said they needed new blood."

As a medical oncologist her speciality is genito-urinary cancers and, as her lengthy resumé testifies, her name is on an exhaustive list of papers and worldwide conference sessions. At present, Sternberg is principal investigator on several major protocols on prostate and bladder cancer, and last year she was elected by her colleagues to the board of the EORTC.

Like most top cancer doctors, her life is a dizzying whirl of international travel, long days and late nights spent writing and reviewing papers, consultancy and faculty positions in Europe and the US – all in addition to running a department.

If the logistics of managing an international career have been well in hand, Sternberg has faced a bit of a struggle with Italian bureaucracy – for example,

her medical oncology accreditation was only recognised relatively recently in the country. But, having started her career at a time when even in the US women were still relatively rare in the world of medicine, she was no stranger to adversity.

It was Sternberg's first professional trip to Europe that was the catalyst for her move from America – in short, she met her husband, top laparoscopic urology surgeon Vito Pansadoro, at a conference and moved to Rome in 1988. Up to that point, she had been set for outstanding success at the Memorial Sloan-Kettering Cancer Center in New York, an institution she considers to be among the best in the world.

"My parents came to the US from Poland during World War Two – they were both professors of mathematics," says Sternberg. "My mother had always wanted to be a doctor, but because of the war this wasn't possible – and it was natural for me to think of becoming one."

Always a good student at school, Sternberg was accepted at the University of Pennsylvania, where she studied psychology and art history – but the notion to become a doctor took hold and she went for it, taking all the maths, physics and other modules necessary to get into the university's medical school. "When I arrived it was the first year they'd had as many as 20% women – there were only a handful before – and it was particularly competitive for us. We were told: 'Look to your right and to your left – one of you will not be here when you finish.'"

Once enrolled, Sternberg loved everything she did – "If I was on a cardiology rotation, I wanted to be a cardiologist; likewise neurology and so on."

After graduation, as an intern at Temple University hospital in Philadelphia, she became slightly

Sternberg has faced a bit of a struggle with Italian bureaucracy

"This has helped me a lot to understand what depressed patients are going through"

disillusioned by general hospital work and switched to psychiatry for a year at the Mount Sinai Medical Center in New York. "This has helped me a lot to understand what depressed patients are going through," she says, adding that at San Camillo she's brought in two psychologists and a psychiatrist as part of the team who routinely work with the cancer patients.

"I think it is a very important part of getting better – it is impossible for either patients or their family not to be scared about cancer, and we can really make a big difference with a multidisciplinary team approach that includes psychologists, psychiatrists, dedicated nurses and volunteers."

With her mentor, Professor Alan Yagoda, at the Memorial Sloan-Kettering Cancer Center in New York

However, after one year of psychiatry training, she transferred to Stanford University to complete her internal medicine training. It was there that she decided to specialise in medical oncology. "Back then there were many physicians who wanted to become surgeons," she says. "Oncology was something people didn't understand and it was a big challenge, and in any case it was also very difficult at that time for a woman to become a surgeon in the US. I wanted to help people who were sick mostly due to no fault of their own and I saw a great need."

Spurred on by the excellent medical oncology department at Stanford – and by a few great women role models – Sternberg returned first to Mount Sinai, then to a fellowship position in medical oncology at Memorial Sloan-Kettering in New York.

There, after being involved with a variety of research projects, she started working under her main academic mentor, Professor Alan Yagoda, whom she had identified as "a brilliant man". "He was head of the solid tumour services at Memorial and his research interest was genito-urinary cancers, which is why I started working in this area."

Sternberg is very much a believer in slow but steady progress. She has seen good advances in cancer treatment since she started her career – "For example, there are patients who are cured today with testicular cancer, and a better understanding of the biology of cancer has led to some breakthroughs in such hard to treat cancers as gastrointestinal stromal tumours. Patients are doing better today because of wider public knowledge about cancer and its symptoms, and screening programmes have led to earlier diagnosis.

"There have been improvements in surgical techniques in addition to the progress that has been made with newer chemotherapeutic agents, and we have better methods of overcoming the side effects of chemotherapy."

An important breakthrough came for Sternberg while working with Yagoda. He had been active in bladder cancer for years, she says, and proposed a new combination of chemotherapy based on his research. However, Yagoda became ill and Sternberg and a colleague, Howard Scher (now chief of genito-urinary oncology at Memorial), took the work forward and developed what has become the "gold standard" for treating relatively fit patients with advanced bladder cancer, namely the M-VAC chemotherapy regimen.

"Before, patients with advanced bladder cancer

either died or lived at most six months," says Sternberg. "We started seeing cures – it was absolutely amazing. The first presentations of this work at the American Urological Association and at the American Society of Clinical Oncology were greeted with both scepticism and enthusiasm by the medical community. However, today no regimen has yet proven to be more effective."

As Yagoda wanted to cut down on his workload, he sent his young colleagues off to international conferences – Scher to Australia and Sternberg to a urology conference in Erice, Sicily. It was her first professional trip to Europe and turned out to be a life changing experience.

"As I was first author on the M-VAC papers, the Europeans were expecting to see an elderly professor and were rather surprised," she says. "Since this was my first important European meeting, I spent a lot of time in my room studying, to make the most of the conference. The last thing I thought was that I'd meet my future husband there."

However, on the last day, at a social event after the meeting, "Vito Pansadoro, a urology professor, asked me to dance. We fell in love on the dance floor, with everyone else stopping to watch. It really happened as though in a fairy tale."

With M-VAC so new, she continued on to London on that European trip to give further talks. "I'll never forget an English physician who asked, 'Would you give your mother this therapy?' and I looked at him and said, 'You don't know my mother – she doesn't listen to anything I say,' and everyone just broke up laughing."

The work on M-VAC brought Sternberg to international attention, but at the Memorial Sloan-Kettering she also worked on kidney cancer – she was head of the interleukin-2 LAK programme there – and on prostate and testicular cancers. So it took a while to wind down her commitments in New York. She got married in 1988 and moved to Italy. She's since been much in demand at many oncology and urology conferences – "There are fewer genito-urinary oncologists than let's say breast cancer specialists," she says. But she doesn't feel her field has a less high profile than breast or lung cancer – certainly not now that prostate cancer has become recognised as one of the most common forms of the disease.

"It's true that prostate cancer was felt in the past not to respond well to therapy," she says. "But more has become known about discovering it earlier, and there has been an important decrease in mortality since there has been widespread PSA [prostate specific antigen] testing. There were two highlighted papers at the plenary session of the American Society of Clinical Oncology (ASCO) conference in June on this disease."

She adds that prostate cancer has also become recognised as a chemosensitive disease, and there is a series of new molecular targeted therapies. "There is plenty of interesting research to be done. We have many protocols running at present for patients with all stages of prostate cancer."

Other studies she has in course include an intergroup protocol on bladder cancer, a US trial where she is the European coordinator, several others with promising molecular targeted therapies and new chemotherapeutic agents for colon, kidney, stomach, breast and lung cancers and melanoma. At San Camillo and Forlanini hospital the major specialist pathologies are gastro-intestinal and lung cancers, while of course Sternberg has been attracting much interest in genito-urinary research. But there was little cancer research of any kind in her department before her arrival at the hospital.

Up until 2002, Sternberg had worked in several hospitals in Rome, first as a medical oncology consultant at the well-known Regina Elena Cancer Institute. As she notes, it is hard to penetrate the Italian health system – there is a lot of bureaucracy in filling public appointments, and she ruffled some feathers by being invited in as a consultant and being sent to international meetings.

After another consultancy position, at Rome's CTO

Out has gone... arcane rules,

such as barring visits from patients' children

Hospital, she became head of medical oncology at a private hospital, the San Raffaele Scientific Institute, which was set up as an offshoot of Milan's hospital of the same name.

Then it was on to San Camillo and Forlanini, one of Europe's biggest hospitals. Sternberg's department is in one of many large, airy but dilapidated pre-World War Two buildings. While she's been promised major refurbishment – and the nearby remodelled emergency and surgical pavilion shows what can be done – she has transformed matters in other ways.

Out has gone an emphasis on very long admissions and arcane rules, such as barring visits from patients' children. Instead, she has put together a team of motivated doctors and nurses, focused on more day hospital treatments, and there's been a turnaround in attitudes towards patient care – as well as enrolment in clinical trials. She's also taken a lead in banning smoking from her department and from the hospital.

Playing the piano with daughter Tatiana

Sternberg has ushered in the kind of infrastructure she'd take for granted back in America – computerised records, proper patient charts, team meetings within the department and multidisciplinary meetings with colleagues in other departments.

At San Camillo, the critical resource is people – she is as yet only halfway through a recruitment programme for oncologists, and like many public hospitals in Europe, the department has suffered major nursing shortages. There's also the problem with a lengthy procedure to appoint staff – and while she works on permanent changes she's even brought in people on her own.

So the staff complement is a mix of official and unofficial personnel, plus volunteers – many of whom are personal friends of Sternberg who are enthusiastic and give their time for free.

She has recruited a Spanish data management specialist with great experience in clinical trial management; another physician, an Italian professor of pharmacology, has returned to Italy after working for more than seven years at the EORTC as a medical data manager in Brussels. These two specialists have been "brilliant in organising the clinical trial work," says Sternberg. In a small way, too, she's also helping to reverse the country's oft-mentioned 'brain drain' – some Italian colleagues have either returned to the country to work with her, or have thought twice about leaving.

Patient rights have been a major issue for Sternberg since coming to Italy. Slowly, she says, the idea of informed consent has taken hold, and cancer has become less of a taboo subject. "There is so much publicity now about new treatments that patients are interested and willing to be involved in trials most of the time. But I firmly believe that willingness depends on how much the doctor is convinced in what he or she is doing."

Fifteen years ago, Sternberg's forthright, American approach may have caused some alarm, such as when, after a liver biopsy, a patient had asked whether his cancer had spread to the liver. "How could you tell him the truth?" asked her colleagues, "We would have said 'we're not sure...' " This attitude has since changed dramatically.

"Truth telling" can differ widely between countries – for example a survey of cancer doctors in northern Italy (published in 2000, in *Supportive Care in Cancer* vol 8, pp 40-45), showed that one-third

With children Tatiana and Vincenzo and husband Vito Pansadoro (*front row*) and brother Harvey (*second row*) and his family in Philadelphia

"The patients know that we are ready to fight with them and they know that they can trust our team"

believed that "patients never want to know the truth". And even a revised version of the Italian "deontology" code allows for some degree of withholding the truth from the patient, if not their family. While strongly defending the need to tell the truth, Sternberg admits to being "softer in her approach than perhaps I was in the US," and the added psychological support she's brought in has been crucial. "The patients know that we are ready to fight with them and they know that they can trust our team." At the hospital, apart from promoting a positive, caring attitude for her staff, she's had to tell patients and concerned family members that they have every right to make appointments with their physicians – but she has had to educate them in proper procedure. There's certainly more calm and order since she has taken over.

There is a tremendous ambition to establish the hospital as a major cancer referral centre, working with colleagues at other important institutions in Italy such as the Regina Elena in Rome. Sternberg is bringing in as many resources as she can muster in the fight against the disease generally, and knows she cannot do this alone.

In addition, she has started a fund-raising organisation, the Samuel and Barbara Sternberg Cancer Research Foundation. "It's named after my parents, because they are responsible for who I am today."

The foundation, set up in 2003, has an impressive list of members and a star cast of world cancer specialists, and "was initiated due to a dire and serious need for the support of cancer patients and research at San Camillo hospital."

Sternberg says that some money has been raised primarily from banks and friends – but ideally she'd like a full-time fund raiser or chief executive on the job. She points to organisations such as the American Italian Cancer Foundation (AICF), which are quite capable of raising a million dollars at fund raising events. The AICF has granted $25,000 to a research fellow who is doing basic scientific research in Italy under Sternberg's guidance.

"My approach to raising money is perhaps American"

"My approach to raising money is perhaps American," she says. "I'd say also that organisations such as the EORTC need to raise funds in Europe for research without upsetting national institutions. They've been hesitant to do this so far, but this kind of work needs to be done by professional fund raisers." Those funds are especially needed, she adds, for trials that may not interest the pharmaceutical companies. She's particularly concerned, along with other members of the EORTC, about the European Union's Clinical Trials Directive, which ostensibly aims to promote multinational trials. But it could pose a threat to non-commercial medical oncology research, one reason being that pharmaceutical companies may be unwilling to supply free, licensed drugs for trials as they could be deemed to be the trial "sponsor", with onerous and costly responsibilities. Sternberg says that there's also a problem for smaller institutions in simply complying with the directive's paperwork. "I have two people working full time on regulatory affairs," she points out – and the worry is that basic academic research in some less fashionable areas may fall by the wayside. She would like to see the rules on translational research clarified as well, noting that "a lot of trials have been done by giving drugs to patients without really studying the biology of the tumours." There is a need for "more collaboration with basic research scientists." Sternberg is building links at present with the Regina Elena Cancer Centre and other research organisations in Italy, and if she gets her wish San Camillo will become a centre for drug development trials and translational molecular research – bridging the laboratory and the clinic. She also has an agreement with La Sapienza University – although San Camillo is not a teaching hospital, physicians who are training to become oncologists now spend time in her department, and she hopes to increase their number.

Seminars and lectures are now playing a part in the day to day life of the department – the intention is also to invite staff from other parts of the hospital so they develop knowledge of oncology and clinical trials. Sternberg is also encouraging her doctors and nurses to attend national and international conferences and is always ready to help them prepare lectures. She recalls her formative period with Alan Yagoda. "The day that I was hired at Memorial he told me that I should take a public speaking course. I never found the time for this, but he helped me anyway, as I practised my first important public lectures with him." After speaking in front of the vast audiences at ASCO, this now holds little fear for Sternberg, but she says she's very hard on herself in preparing talks. "I take lectures seriously and make sure that each one is different, even lecturing in Italian." She says that the secret is very simple: "You have to study if you want to be prepared."

On top of all this, she has a very busy family life. Sternberg is also a mother of two children. "Vincenzo and Tatiana are my pride and joy." And she puts being a good mother as her top priority, although time is an issue (a card from Tatiana on her office wall asks her not to go to so many conferences...). She drives her children to school every day and is not willing to give up that precious time with them in the mornings, and she is always ready to help them with their homework if needed.

It's certainly hard not to be impressed by Sternberg's personal life. Her home is a villa just outside Rome, which was in her husband's family. It has a beautiful garden and simple but genuine Italian food is served. Like many Romans, they escape the city each August sailing, with Vito as captain and Cora as first mate. Sternberg is well established in Rome now – last year she received an award from the American International Club of Rome for her achievements in the Italian healthcare system.

The worry is that basic academic research in some less fashionable areas may fall by the wayside

"When I think back, I believe the Italian medical community did not quite know what to make of me"

"When I think back, I believe the Italian medical community did not quite know what to make of me," she told the audience at the awards dinner. While not one to seek media attention, she's been featured by the BBC in rebutting the claims made in 1998 for a "miracle" cancer treatment by Dr Luigi Di Bella (and since disproved by the Italian government). She is a little wistful when she thinks about the kinds of facilities and opportunities that are available for research in America, but has made a major commitment to her family and to making things work in Italy. As she says, her present work-life balance in Rome would be hard to replicate in New York. "I also don't think that I would have been able to have made all the contacts that I have in Europe if I'd stayed in America. Europe and my European colleagues have been good to me – and the EORTC has been particularly open towards me since my arrival." She draws strength from women role models such as Eleanor Roosevelt, Margaret Thatcher and Hillary Clinton – she's an avid biography reader of such individuals – but apart from Alan Yagoda, she cites only her husband, Vito, and her parents as mentors in her life.

"Vito taught me that the glass is always half full rather than half empty," she says. As Vito Pansadoro is a surgeon, she adds, there is no professional tension in the family.

In their work, they have established a collaborative approach to cancer treatment, although they have to be careful not to discuss medicine too much at the dinner table.

For the refurbished oncology department at San Camillo hospital, Sternberg would like to make it a place that people want to visit rather than run away from. "This will be done by employing the proper use of colours and space and perhaps by inviting artists to paint – it should be bright and cheery," she says. Given the preponderance of art in the city, this is certainly doing things the Roman way.

Cancer in the year 2025

Olivia Timbs and Karol Sikora

How will cancer look in the year 2025? More than fifty UK cancer care specialists – physicians, scientists, health managers, economists, health service watchers – together with cancer charities and patients spent two days together in late 2003 asking themselves this question. Here is what they came up with.

In 2025 over three million people in the UK will be living with cancer. Like diabetes, heart disease and asthma, cancer will become one of the major chronic diseases that impact on the way people live but do not inexorably lead to death. The model will be prostate cancer, which men tend to live with, rather than die from. Progress will be made in preventing cancers and even greater progress will be made in understanding its myriad causes and in detecting, diagnosing and treating the disease. Refinements of current technologies and techniques – in imaging, radiotherapy and surgery – together with the availability of targeted drugs will make cancer a controllable disease.

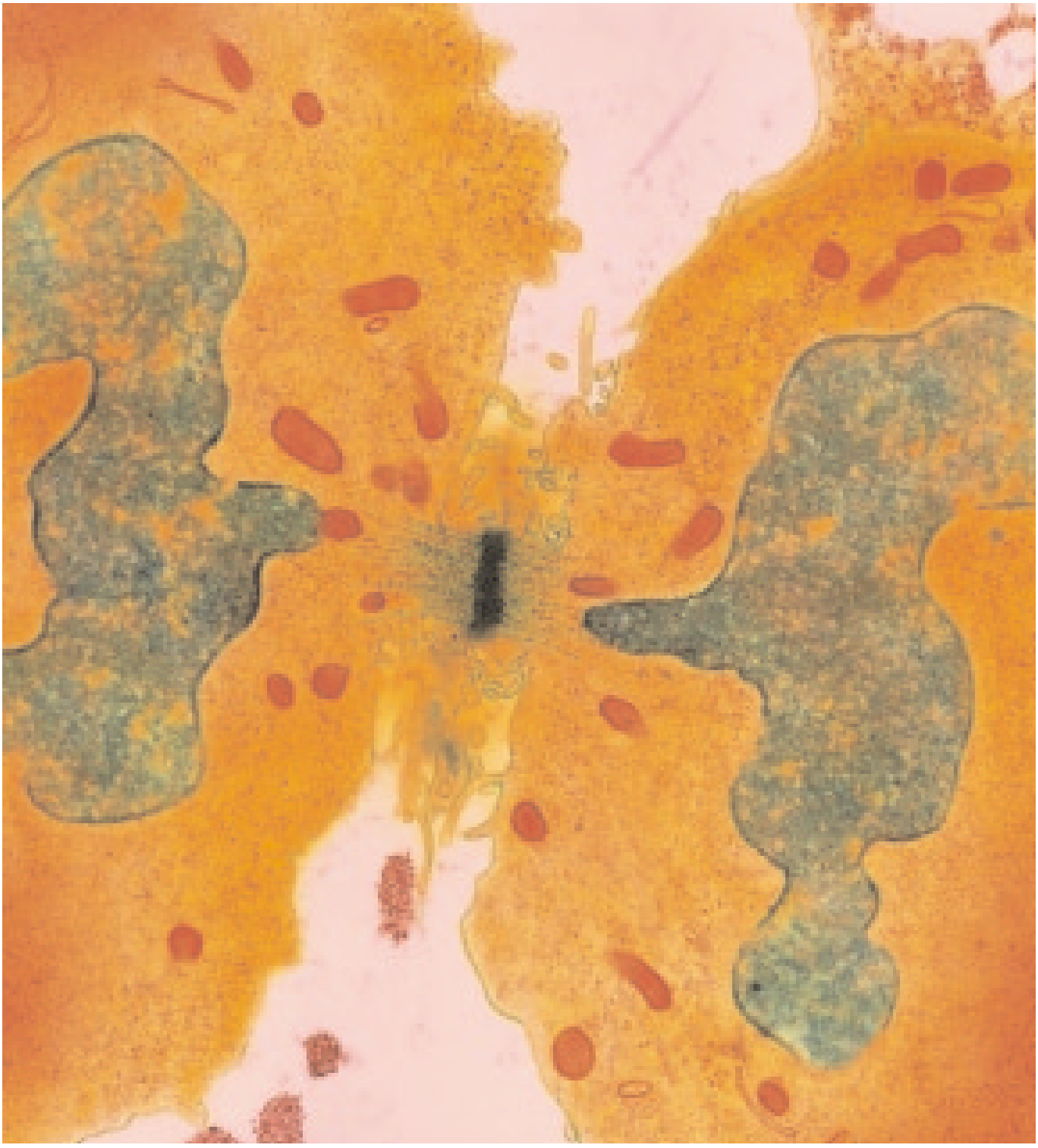
Cure will still be sought, but will not be the only satisfactory outcome. The fear that cancer kills, still prevalent in the early years of the 21st century, will be replaced by an acceptance that many forms of cancer are simply a consequence of old age.

With the increase in demand for treatment, the cost of cancer care is expected to soar, creating immense challenges for health services. While in 2025 more patients will benefit from better diagnosis and new treatments, technology will also bring greater inequality to the health sector. It is unrealistic to assume that the best care possible will be offered to all patients irrespective of their socio-economic circumstances. Well-informed patients, with adequate funds, will ensure that they have rapid access to the newest and best treatments. Many of these will take place close to patients' homes using mechanisms devised by innovative service providers.

Clinicians in Europe will continue to be dependent on technologies primarily designed for the world's major health market – the United States – which, with 5% of the world's population, consumes nearly 55% of cancer medication. Targeted niche drugs will be less appealing to industry as the costs of bringing each new generation of drugs to the market will not match the returns from current blockbusters. Intraprofessional boundaries will blur – doctors from traditionally quite distinct specialties may find themselves doing the same job. And clinical responsibilities will be assumed by health professionals without medical qualifications. All professionals are likely to find challenges to their territory hard to accept. But new ways of working need to be developed soon, as the leaders of the health professions of 2025 – doctors, nurses, pharmacists and their support staff – are already in training.

Prevention and screening

At the beginning of the 21st century, 10 million people in the world developed



SPL / GRAZIA NERI

Coloured transmission electron micrograph (TEM) of a section through a cancer cell undergoing mitotic cell division

WHAT DO YOU THINK?

Will fear and anxiety be mitigated?

Will the focus be increasingly on control, not cure? Should it?

Will we have a generation of elderly living with chronic cancer, treated as outpatients and supported by ever-dwindling numbers of carers?

Will patients rely on other patients to guide them through treatment options?

Are we training for specialisms that have no future in their current form?

Will the cost of drugs bring national health systems to their knees?

Send your comments to Kathy Redmond, Editor, Cancer World, at magazine@esoncology.org or fax them to +39 02 43359640

cancer each year. The cause of these cancers was known in roughly 75% of cases: 3 million were tobacco related; 3 million were a result of diet; and 1.5 million were caused by infection. Anti-smoking initiatives were considered to be successful – although it took 50 years from the time the association between smoking and cancer was first identified. In the UK, 80% of the population smoked in the 1960s; in 2003 the figure fell to 30%, but masked real health inequality (the percentage of smokers in the higher socio-economic bracket fell to single figures, while remaining around 50% in the lower socio-economic bracket). Banning smoking in public places will lead to a further drop of about 4%.

Lessons from anti-smoking initiatives will be instructive for prevention in the future. Although the link between poor diet, obesity, lack of exercise and cancer has not yet been confirmed, there is sufficient circumstantial evidence to suggest that strong associations will be found. Long before 2025 there will be bans on advertising for crisps, sweets and soft drinks on television.

A health tax on these products will be introduced and sponsorship of public events by manufacturers of these products will be banned. By 2010, obesity among the middle classes will be socially unacceptable, but will remain common among the economically disadvantaged.

The future prevention picture will be coloured by post-genomic research. In 2003, it was accepted that about 100 genes were associated with the development of a whole range of cancers. Carrying a changed version of a particular gene – or combination of changed genes – will not necessarily lead to the development of that cancer but will increase the risk. By 2025 most people will be genetically mapped. The information – gained from a simple blood test – will be easily stored on a smart-card. Legislation will be required to prevent this information being used to determine an individual's future health status for mortgage, insurance and employment purposes. However, the process of mapping and screening will reveal a predisposition to certain diseases and people will have to learn to live with risk.

In the early years of the 21st century, the average age of diagnosis of cancer was 68. This figure is expected to fall by 2025 as a result of improvements in screening, detection and diagnosis. Predisposition for certain cancers which tend to manifest themselves when the patient is 70 or 80, will be detected in young adult life and corrected successfully when the patient is 30. And while increasing age will remain the strongest risk predictor, the computing power of the future will bring accurate calculation of risk factors, and predictions will take place on an unimaginable scale. Screening programmes will be developed on a national basis and novel providers of risk assessment services are likely to emerge.

Detecting cancer

By 2003 it was established that cancers were fundamentally somatic genetic diseases that result from several causes: physical, viral, radiation and chemical damage. Other processes – chronic inflammatory change, immuno-surveillance and failure of apoptosis, were also implicated. By 2025 cancer will no longer be understood as a single entity – it will be considered to be a cellular process that changes over time. In 2003 most diagnoses of cancer depended on human interpretation of changes in cell structures seen through a microscope. By 2025 microscopes will be superseded by a new generation of scanners that detect molecular changes and can build

THE NEW DIAGNOSTICS

- Radiology and pathology will merge into cancer imaging
- Dynamic imaging will create a changing image of biochemical abnormalities
- Cancer changes will be detected prior to disease spread from primary site
- Greater precision in surgery and radiotherapy will be used for pre-cancer
- Molecular signatures will determine treatment choice

a picture of change over time, imaging cellular activity. We will have the ability to probe molecular events that are markers for early malignant change.

Imaging and diagnosis will be minimally invasive and enable the selection of the best and most effective targeted treatments. Even better imaging will be able to pick up pre-disease phases and deal with them well before they are currently detectable. These techniques will also be crucial to successful follow-up. A patient who has a predisposition to a certain cancer process will be monitored regularly and treatment offered when necessary. Not all cancers will be diagnosed in these early stages – some patients will inevitably fall through the screening net. Nevertheless, there will be opportunities to offer less invasive treatment than at present. Surgery and radiotherapy will continue, but in greatly modified form, as a result of developments in imaging. Most significantly, surgery will become part of integrated care. Removal of tumours or even whole organs will remain necessary on occasion, but the surgeon will be supported by 3-D imaging, radio-labelling techniques to guide incisions and by robotic instruments. And although many of the new treatments made possible by improved imaging will be biologically driven, there will still be a role for radiotherapy – the most potent DNA damaging agent – in treating cancer with great geographical accuracy.

In 2025 most cancer treatments will be able to be performed on an outpatient basis. Minimally invasive treatments will reduce the need for long stays in hospital and the need to provide care close to where patients live will be both desirable and possible. Highly sophisticated scanning equipment and mobile surgical units will be transported to where they are required. Technicians, surgical assistants and nurses will provide the hands-on care, while technical support will be provided by the new breed of clinician – a disease-specific imaging specialist working from a remote site. Cost control will be an essential component of the diagnostic phase.

New treatment approaches

In 2025 eradication of cancer, although still desirable, will no longer be the primary aim of treatment. Cancers will be identified earlier and the disease process regulated in a similar way to chronic diseases such as diabetes. Surgery and radiotherapy will still have a role depending on the type of cancer, the stage at which the disease is identified and the performance of new drugs, but treatment will be less aggressive.

By 2025, cancer treatment will be shaped by the new generation of drugs. What they will look like is not yet apparent and will depend on the success of agents currently in development. Over the next three to five years, we will understand more fully what benefits compounds such as kinase inhibitors are likely to provide. It is estimated that in 2003 around 500 oncology drugs were being tested in clinical trials. Of these, around 300 were against specific molecular targets. This number is set to rise dramatically. Two thousand compounds will be available to enter clinical trials by 2006 and 5,000 by 2010. Many of the drug candidates will be directed at the same molecular targets, and industry is racing to screen those most likely to make it through the development process.

So what will these drug candidates look like? In 2003, small molecules were the main focus of research – most of them designed to target specific gene products that control the biological processes associated with cancer, such as signal transduction, angiogenesis, cell cycle control, apoptosis, inflammation, invasion and differentiation. Treatment strategies involving monoclonal antibodies, cancer vaccines and gene therapy are also being explored. While there is great confidence in the efficacy of these targeted agents, their overall efficacy at prolonging survival is more uncertain. Many could just be expensive palliatives.

We are already seeing the emergence of drugs targeted at a molecular level – Herceptin (trastuzumab), directed at the HER2 protein, Glivec (imatinib), which targets the Bcr-Abl tyrosine kinase, and Iressa (gefitinib) and Tarceva (erlotinib), directed at EGFR tyrosine kinase. What will be important in 2025 is whether a cancer has particular biological or genetic characteristics. Traditional categories will continue to be broken down and genetic profiling will enable treatment to be targeted at

In 2025 eradication of cancer...

will no longer be the primary aim of treatment

the right patients. Patients will understand that treatment options will depend on their genetic profile and the risks and benefits will be much more predictable than today.

Therapies will emerge through our knowledge of the human genome and the use of sophisticated bio-informatics. Targeted imaging agents will be used to deliver therapy at the screening or diagnostic stage and technology will enable the disease process to be tracked much more closely. Biomarkers will allow clinicians to measure whether a drug is working on its target and, if it is not, an alternative treatment strategy will be sought. Tumour regression will become less important as clinicians look for molecular patterns of disease and its response.

Barriers to the introduction of new treatments

Innovation in cancer treatment is inevitable. However, there are certain prerequisites for the introduction of new therapies. The therapies must be deliverable to the right biological target, and to the right patient, in a way that is acceptable to patients, healthcare professionals and society. Innovation must also be marketed successfully so that professionals, patients and those picking up the cost understand the potential benefits. The explosion of new therapies in cancer care is going to continue and costs will remain high. The cost of cancer drugs in 2003 was estimated to be $21bn globally, of which $14bn was spent in the United States. If effective drugs emerge from the research and development pipeline, the cancer drug market could reach $300bn globally by 2025, with the cost spreading more widely around the world.

But parallel to this explosion in therapies and increase in costs, a number of confounding factors will make markets smaller. Technology will reveal which patients will not respond to therapy, thus making blockbuster drugs history. Doctors will know the precise stage of the disease process at which treatment is necessary. And as cancer transforms into a chronic disease, there will be more co-morbidities and associated drug-drug interactions.

How do we balance this equation? There is a risk that pharmaceutical companies will stop developing drugs for cancer and focus instead on therapeutic areas where there is less individual variation and more scope for profit. Development costs are also rising. Ten years ago, the average cost of developing a new cancer drug was around $400m. In 2003, it was $800m. At this rate of growth, the cost of developing a new drug in 2025 could rise to $2bn. With this in mind, the process of developing drugs needs to be made faster.

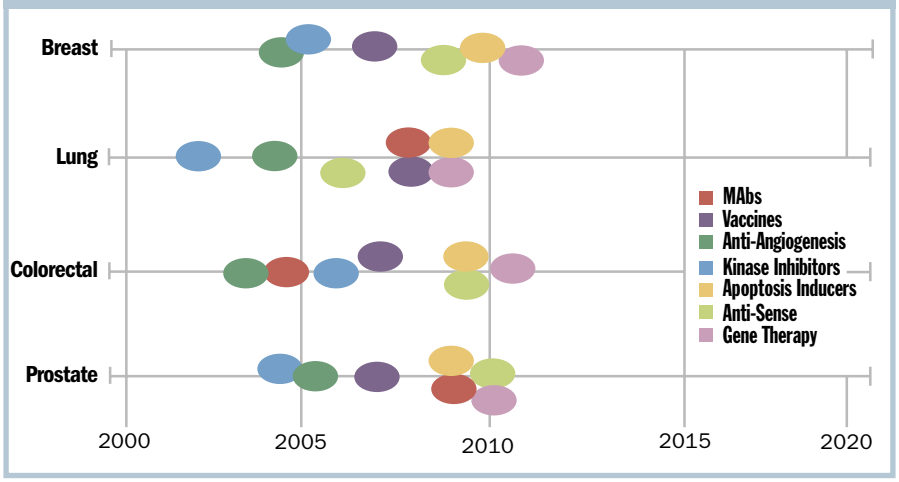
However, instead of research being made simpler, changes in legislation concerned with privacy and prior consent are making it more difficult.

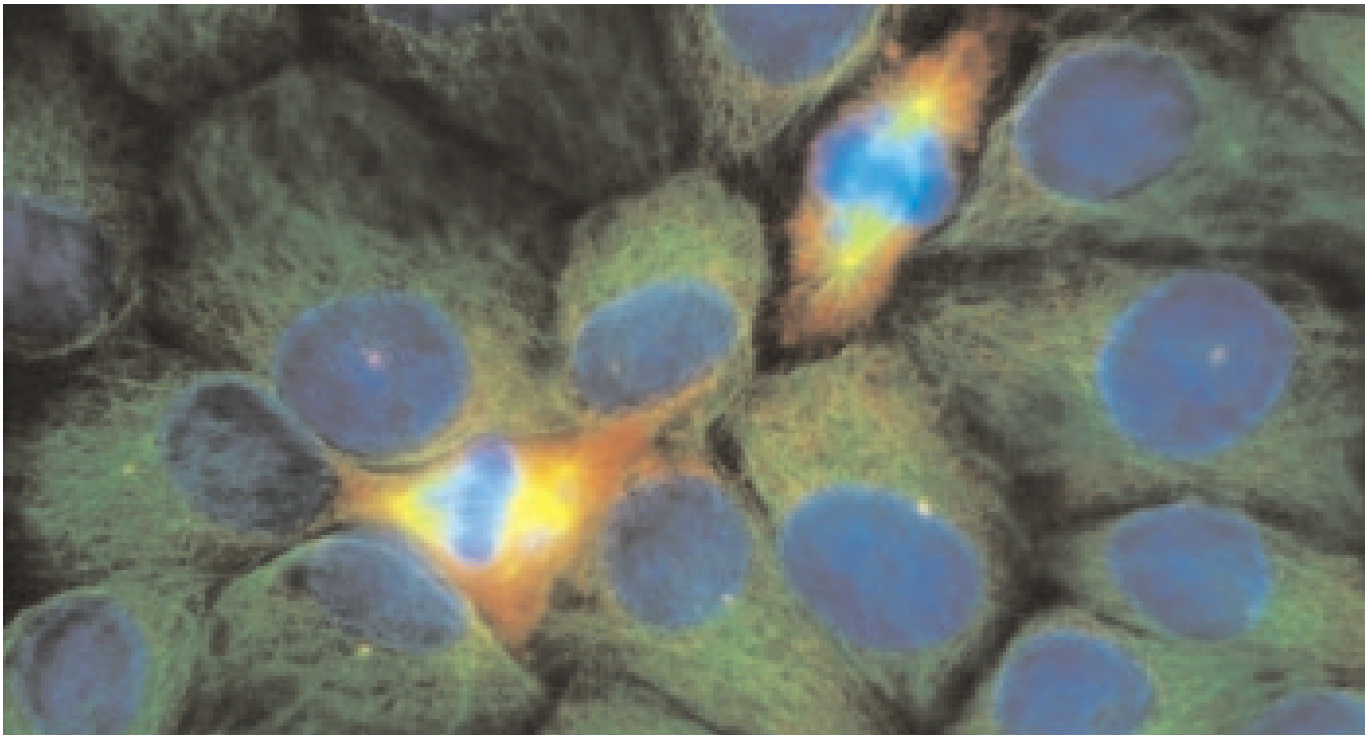
The EU Clinical Trials Directive will make quick hypothesis testing trials impossible. To overcome such constraints regulators will have to start accepting surrogate markers rather than clinical outcomes when approving therapies. Outcome studies may well move to post-registration surveillance of a drug's efficacy similar to cholesterol-lowering agents today. The rise of personalised medicine will mean the temptation to over-treat will disappear. Doctors and patients will know whether a particular treatment is justified. The evidence will be there to support their decisions. As a consequence of this, treatment failure – with all its associated costs – will be less common.

BARRIERS TO INTRODUCING NEW THERAPIES

- The drug industry will continue to compete for investment in a competitive, capitalist environment
- Blockbuster drugs drive profit – niche products are unattractive in today's market
- Personalised therapies are difficult for today's industry machine
- Surrogate endpoints will be essential to register new drugs

PREDICTED NEW DRUG APPROVAL DATES FOR MOLECULAR THERAPIES IN THE USA





SPL / GRAZIA NERI

Immunofluorescent Light Micrograph of *squamous carcinoma* cells, cultured from a tumour

At this rate of growth, the cost of developing a new drug in 2025 could rise to $2bn

The patient's experience

Two separate developments will determine the patient's experience of cancer care in 2025 – increased expectations of patients and targeted approaches to diagnosis – both of which will individualise care. Patients will take more responsibility for decisions rather than accepting a paternalistic "doctor knows best" approach. This will partly be fuelled by the Internet and competitive provider systems. With patients having access to a wealth of health information, they will need help in assessing risks and benefits and determining what is best for them. Hence we will have patient brokers who will act as independent advocates guiding patients through treatment options.

Cancer care will be a two-way street. Patients will coach doctors and other patients. With so many people expected to be living with cancer in 2025, they will have a great deal of knowledge and experience that professionals will need to access. There will be continued interest in complementary medicines covering a wide range of talking, touching and pharmacological therapies operating outside the norms of conventional medical science. Improved regulation of practitioners in this area will enhance the quality of care provided and lead to better organisation of services.

Care in the early stages will be provided near the patient's home. Even the most sophisticated diagnostic machinery or robotic surgeon will be mobile. When cancer centres developed in the mid 20th century, the disease was relatively rare and survival low. In 2025, cancer will be common and when in-patient care will be required, patients will be able to be treated at a 'cancer hotel'. For many, that option will not be necessary as most new drugs will be administered orally, enabling the patients to be treated in their communities. The new

EXPERIENCING CANCER IN 2025

- Patient brokers will guide people with cancer through the system
- Choice will be real and will involve cost decisions
- Patients will make a contribution to their care costs
- Complementary therapies will be widely available and well regulated
- Themed death chosen by patients will be possible

approach, however, will place a huge burden on social services and families, necessitating psychological and physical support systems.

In 2003, 70% of the cancer budget was spent on care associated with the last six months of people lives. Although many recognised that such treatment had more to do with the management of fear rather than the management of cancer, medical professionals had relatively few treatment options available and there was limited awareness of which patients would benefit. There was also an institutional reluctance to destroy patients' hopes that led to confusion between the limits of conventional medicines and a reluctance to face the inevitable – by patients, their families and doctors.

By 2025 much of the fear associated with cancer in the past will be mitigated. Pain relief and the control of other symptoms associated with cancer treatment will be much improved. Demand for treatments with few side-effects or lower toxicity will be high, even if there are only quite modest survival gains. While, previously the transition between active and palliative care was often sudden, in 2025, because patients will be in much greater control of their situation, the change in gear will not be as apparent. More patients will choose where they die and the manner of their death. Euthanasia will be legal, but it will not be a majority choice, because distressing symptoms will be better controlled. Indeed a themed death may be a realistic option. In 1900, 90% of people died at home. By 1950 the figure had dropped to around 50%. In 2003, only a quarter of cancer patients died at home. In 2025 the percentage of people dying at home will climb again. This will be driven by patient choice, better communication between health professionals and increased domiciliary services.

Professional reconfiguration

One of the greatest challenges to providing the best cancer care in 2025 will be having the right people in the right jobs. Henceforth it will be essential not to continue to train people for jobs that no longer exist. In 2025 barriers between health care professions will be broken down in order to enable delivery of the new approaches to cancer care. Intra-professional barriers will disappear. The work of pathologists and radiologists will become one as their traditional skills are augmented by the new generation of diagnostic and treatment devices.

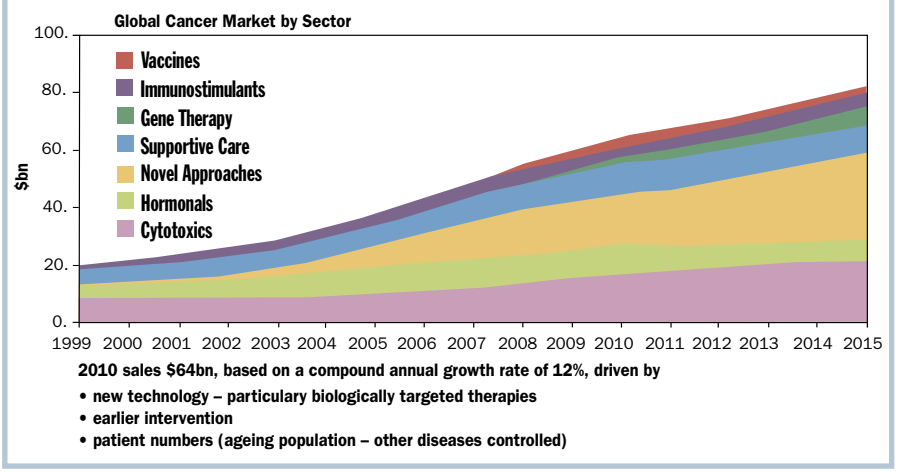
Oncologists will find that many forms of chemotherapy will be delivered with the aid of the new technology, and surgeons will be using robots to enable them to operate. Fewer highly trained specialists will be required, since much of their responsibility will be delegated to specialist technicians and nurses working to protocols, and mobile technology will enable them to work at a number of sites on the same day.

Conclusion

In 2025 cancer will become incidental to day to day life. It will not necessarily be eradicated but it will not cause the same anxiety as previously. Patients in all socio-economic groups will be better informed and have far greater control over their medical destinies. Surgery and chemotherapy will not be rationed on grounds of age since all interventions will be less damaging psychologically as well as physically.

How true this picture will be will depend on whether the technological advances outlined in previous sections

CANCER MARKET SET TO TRIPLE BY 2010



will emerge. The ideal in terms of cancer care will exist for a minority of patients, but the majority may not have access to the full range of services. Old people in 2025, having been relatively poor all their lives, may suffer from cancer and a huge range of co-morbidities that will limit their quality of life. Will there be enough young people to provide the care needed by the old? As with all health issues, the question of access will be determined by cost and political will.

Conservatively, with patients living longer with cancer, rather than dying from it, and with access to new technologies, cancer care costs could increase fivefold (from £20,000 per patient per year in 2003 in the UK to £100,000) and thus absorb a hefty chunk of a country's health care budget. On the plus side, although the technology will be expensive, it will be used more judiciously, as it will be better targeted, and though costs will increase for treating each individual patient, the overall costs will decrease because more care will be delivered at home. At the same time, because people will live longer the life-time costs of cancer care will rise along with co-morbidity costs. Politicians will be faced with a real dilemma: if the prevalence of cancer increases, the cost of delivering care could be massive. Will cancer care need to be rationed in a draconian way?

One dilemma in 2025 will be the political power of old people. Old people will live longer and will wield considerable influence. This educated gerontocracy will have high expectations and will demand high standards of care. Will a tax-based health system be able to fund their expectations? Politicians will have to consider the alignment between patients' requirements and the wishes of taxpayers and voters, for as the population ages the percentage of tax-paying voters will fall. Will the younger taxpayers of 2025 tolerate the expensive wishes of non-taxpayers? The interests of voters may be very different to the interests of taxpayers. It seems likely, therefore, that the days of an exclusively tax-funded health service are numbered. Co-payments and deductibles will be an inevitable part of the new financial vocabulary.

Whatever system is put in place there is the prospect of a major socio-economic division in 2025. A small percentage of the elderly population will have made suitable provision for their retirement, both in terms of health and welfare, but the vast majority will not be properly prepared. Policy-makers need to start planning now. The most productive way forward is to start involving cancer patient and health advocacy groups in the debate, to ensure that difficult decisions are reached by consensus. Societal changes will also leave a greater percentage of old people alone with no psychological crutch to lean on at the onset of serious illness, and there will be a global shortage of carers – the unskilled, low-paid but essential component of any health delivery system. The richer parts of the world are now harnessing this from the poorer, but eventually the supply of this precious human capital will evaporate.

New financial structures will emerge with novel consortia from the pharmaceutical, financial and healthcare sectors, enabling people to buy into the level of care they wish to pay for. Hospitals will become attractive health hotels run by competing private sector providers and global franchises will provide speciality therapies through these structures.

Governments will have long ceased to deliver care. In Britain the NHS, one of the last centralised systems to disappear, will convert to UK Health – a regulator and safety net insurer – already by 2012.

What will be important in 2025 is whether a cancer has particular biological or genetic characteristics

The ability of technology to improve cancer care is assured. But this will come at a price – the direct costs of providing it and the costs of looking after the increasingly elderly population that will result.

We will eventually simply run out of things to die from.

New ethical and moral dilemmas will arise as we seek the holy grail of compressed morbidity. Living long and dying fast will become the mantra of 21st century medicine. Our cancer future will emerge from the interaction of four factors: the success of new technology, society's willingness to pay, future healthcare delivery systems and the financial mechanisms that underpin them.

The authors thank the Amberstone Family Trust and Cancer Relief Macmillan Fund for their support for the meeting.

Cancer vaccines – hope or hype?

Anthony Walker*

There have been many false dawns in the field of cancer vaccines, but some of the new products look distinctly promising.

Using vaccines that stimulate the immune system to fight cancer appeals to many as a natural approach that is both safe and effective. And, judging from a recent headline in the UK newspaper *The Times* – "Vaccine jab could cure lung cancer" – there is clear public interest in this area. Even big pharma is showing signs of excitement. At a partnering conference one of the more traditional majors said cancer vaccines had moved from the 'no strategic interest' category to 'watchful waiting' – an almost seismic shift to those of us who remember past scepticism. But is there promise beyond the hype? And can vaccines find a place in modern cancer therapy?

The immune system has always played an important role in cancer prevention. Pre-malignancies, induced by toxic chemicals, excessive exposure to UV radiation, viral infection or simply spontaneous genetic mutations, arise at intervals throughout the body. They are generally detected and destroyed by a panoply of immune mechanisms, mostly before we are aware that anything untoward has happened. On rare occasions, this occurs after the clinical manifestation of cancer, resulting in spontaneous regressions. Vaccine treatment aims to harness these mechanisms in a therapeutic setting.

The prospect of avoiding the severe side-effects associated with many treatments underpins the demand for cancer vaccines. Despite recurrent vaccine hysteria, safety, selectivity and potency remain the hallmarks of a vaccine, and cancer vaccines promise efficacy with limited – or no – side-effects. Serious adverse events have been the exception in the clinical trials of experimental vaccines conducted to date. At the same time, there have been few glimpses of real benefit, with numerous false dawns and much disappointment.

But there was an explosion of interest in this field after the unravelling of mechanisms for triggering cytotoxic T-cell (CTL) response about 15 years ago. It was a fundamental breakthrough in immunology that provided insights into the workings of the immune system and how to activate and direct it to attack cancers. Moreover, our knowledge of how cancers, in turn, deploy defence mechanisms to evade or disable the immune system has also increased.

Cancer vaccines can be divided into three categories. The first group, non-specific immunostimulants, covers the agents BCG, interleukin-2 and interferon alpha, which are used to treat bladder cancer, renal cell carcinoma and malignant melanoma. They boost levels of activity in the immune system to reverse immunosuppression induced by the tumour, resulting in rejection of the cancer. Although many agents have been tested, few have been successful and these failures have tarnished the entire field.

Specific-target vaccines are based on the antigens expressed by tumours but not by normal tissues. There are numerous variants: subunit and anti-idiotype vaccines and immuno-gene therapy to name but three. Much effort has been directed toward high-tech solutions in this area, but it has become apparent that tumours continue to mutate as the disease progresses, evading the immune system by downregulating or losing the expression of the target antigen.

The third group, multivalent and ultravalent vaccines, combine several antigens in one formulation to overcome immunological evasion. This is akin to combination chemotherapies, whereby resistance to one element is mitigated by the presence of others. Taking this concept still further, a number of vaccines use inactivated whole cancer cells because they contain the entire spectrum of tumour antigens in an ultravalent formulation.

Cell vaccines

The most encouraging results so far have come from cell vaccines. These have moved the state of the art beyond safety and immunogenicity into the realm of clear clinical benefit. Indeed, in 70 recently published vaccine trials, half used cell therapies (late-stage clinical highlights are shown in the box).

Broadly speaking, there are two types of cell vaccine: patient-tailored (autologous) and off-the-shelf (allogeneic). The autologous approach involves harvesting patients' tumour and immune cells, processing them ex vivo to induce immuno-

logical activity and then returning them to the donor. Companies using autologous tumour cells include German firm LipoNova, California-based Cell Genesys, Avax Technologies from Kansas and Intracel from Maryland.

From a scientific standpoint, autologous cell vaccines have significant merit, matching the tumour antigens precisely to the patient being treated. They have also produced favourable results in trials of several cancers. But interest in this approach has waned because of inherent logistical difficulties and the associated high costs.

The other autologous technology employs patients' immune cells. Dendreon, IDM from Paris, France, Merix from North Carolina and Geron, based in California, use dendritic cells (DCs), whereas Xcyte and Targeted Genetics, both of Seattle, Washington, use T-cells. Again, this approach is scientifically and medically sound, but doubts remain as to whether the treatments can be applied across broad patient populations.

Allogeneic cell vaccines rely on the cancer antigens present in a high percentage of tumour types. Although the spectrum of tumour-specific and tumour-associated antigens (TSAs and TAAs respectively) will be unique to a tumour deposit, some cell lines express tens if not hundreds of common antigens at high frequency. When immortalised, these cell lines can be used in vaccines. They grow indefinitely in culture systems and can be manufactured at industrial scale in modern cGMP facilities.

Another advantage of allogeneic cell vaccines is that the concept behind them – they are a product in a bottle rather than a bespoke service – is familiar to the pharma industry. Furthermore, the costs are lower from economies of scale and, importantly, they are readily available (there are no lengthy lead times as there may be with certain autologous systems).

The leading proponent of this approach is Dr Donald Morton, founder of CancerVax and a pioneer in clinical cancer immunotherapy for more than four decades. CancerVax's lead product, Canvaxin, is composed of three human melanoma cell lines rendered replication-incompetent through irradiation, with BCG used as a vaccine adjuvant for the initial two doses. Canvaxin, which is currently in two international randomised Phase III trials in malignant melanoma, has arguably produced better safety and clinical efficacy data than those supporting the approval of several new cancer therapies.

Other companies active in this area include Cell Genesys (which also has autologous-vaccine programmes) and London-based Onyvax, whose lead product for prostate cancer, Onyvax-P, is in Phase II trials, data from which will be reported later this year.

Next steps

The field of cancer vaccines has matured considerably over the past few years. Several products are in Phase III trials with the prospect of potential product registrations over the next 18 to 24 months. If all goes to plan, vaccines could be available to patients in 2006 or 2007.

Although significant challenges and risks remain – as they will until the first cancer vaccine is registered – these have shifted away from the early proof-of-concept issues towards the practical realities of manufacturing and regulatory affairs.

This, together with compelling data from late-stage trials, is convincing the sector that cancer vaccines represent much more than hype.

*Anthony Walker is CEO of Onyvax, a London-based biotechnology company which develops novel cancer therapies that harness the body's immune system.

RECENT TRIAL RESULTS

RCC Vaccine (LipoNova). The renal-cell carcinoma vaccine was tested in a 55-centre, 558-patient trial. At 70 months, progression-free survival rates were 72% in the vaccine group and 59.3% in the control group. The product was well tolerated, with only 12 adverse events associated with the treatment.

Canvaxin (CancerVax). In a sample of 263 patients who underwent complete resection of clinically detectable stage IV melanoma, 150 people received post-surgical treatment with Canvaxin in Phase II protocols and 113 received other or no adjuvant therapy. Median overall survival and five-year overall survival were significantly increased in patients who received the treatment vaccine compared with those who didn't (36 compared with 18 months, and 39% compared with 19%).

Provenge (Dendreon). In a randomised Phase II/III trial in hormone refractory prostate cancer, patients receiving Provenge had a significant survival advantage, with an 89% average overall increase in survival time compared with the placebo group. Median survival time in the treatment group was 30.1 months compared with 22.3 months among people who were not treated. At 30 months from randomisation, the survival rate for Provenge-treated patients was 3.7 times higher than for those receiving placebo.

This article was first published in Scrip Magazine, May 2004 (134, 6-7). Reproduced by permission of PJB Publications Ltd.

New law boosts EMEA role

Kathy Redmond

The new European pharmaceutical legislation came into force on 20 May. Its effect is to considerably enhance the role of the European Medicines Agency (formerly the European Medicines Evaluation Agency – it retains its acronym 'EMEA') in a number of areas. These include the provision of scientific advice to companies; giving opinions – in co-operation with the World Health Organization – on the use of medicines outside the European Union; and giving opinions on the compassionate use of unapproved medicines in Member States.

Under provisions which are due to be implemented in November 2005, EMEA will also take on a role in conditional approvals and fast-track reviews, and the scope of the centralised approval procedure will be extended in such a way that it covers all cancer drugs.

The Agency was also given a stronger role in the provision of information to patients and the public, including a mandate to develop a database of all medicines approved in the European Union ('EuroPharm'). Small- and medium-sized companies should benefit from provisions in the legislation enabling EMEA to offer them administrative and scientific support.

Other changes brought about by the legislation include:

- The Committee for Medicinal Products for Human Use replaces the Committee for Proprietary Medicinal Products. The new Committee will be known as the CHMP.
- A new Committee for Herbal Medicinal Products is created and is expected to begin activity later in 2004.
- The composition of the Management Board changes from two to one member per Member State, in addition to two representatives each of the European Parliament and the European Commission. They are joined by two representatives of patient organisations, one representative of doctors' organisations and one representative of veterinarians' organisations.

OVER THE PAST FEW MONTHS a number of cancer drugs have received EU marketing authorisation, including Velcade (bortezomib), Faslodex (fulvestrant) Photobarr (porfimer sodium) and Erbitux (cetuximab).

■ ■ ■

ELI LILLY'S ALIMTA (pemetrexed), indicated for the treatment of malignant pleural mesothelioma and non-small cell lung cancer, has received a positive opinion from the CHMP.

■ ■ ■

TWO OF ROCHE'S ONCOLOGY PRODUCTS have had their indications extended by the CHMP. One of these is MabThera (rituximab), which can now be used in previously untreated patients with indolent non-Hodgkin's Lymphoma in combination with CVP (cyclophosphamide, vincristine and prednisolone) chemotherapy. The other is Herceptin (trastuzumab), which is now indicated for use in combination with docetaxel for the treatment of patients with HER2-positive metastatic breast cancer who have not received prior chemotherapy for metastatic disease.

■ ■ ■

NOVARTIS HAS SUBMITTED marketing authorisation applications in the United States, European Union and Switzerland for the use of Femara (letrozole) in the extended adjuvant treatment of early breast cancer in postmenopausal women who have completed standard adjuvant (post-surgery) tamoxifen therapy and remain disease-free.

■ ■ ■

PHARMION CORPORATION has withdrawn its European marketing authorisation application for thalidomide for the treatment of multiple myeloma, and will now focus on preparing a new dossier containing the additional clinical data requested by EMEA. Thalidomide will continue to be available in Europe on a compassionate use basis. The agent is already approved in Australia, New Zealand and Turkey for the treatment of relapsed/refractory multiple myeloma.

Secrets of success

Interview by Raphaël Brenner

In the world of oncology drugs, Roche is one of the giants. Here, Chief Executive **Franz Humer** talks about the research and business strategies behind his company's success, and about novel therapies in the pipeline that could help alleviate patients' experience of cancer. He also speaks of his mission to save Europe from relegation in the field of medical research.

Austrian-born Franz B. Humer, Chairman and Chief Executive of Roche, has good reason to be happy. His company, based in Basel, is a world leader in cancer drugs and diagnostics, and he believes it holds one of the most exciting drug pipelines in the industry. Roche's success story is the outcome of shrewd strategic choices initiated in the late 1980s. "It is very important to see how science has developed in the last 10 years," says Humer. "The unravelling of the human genome has allowed biomedical research to make quantum leaps in oncology and because Roche was at the forefront of research, it was able to apply the new knowledge faster than others."

Several factors explain Roche's success. Very early on it decided to tackle the field of oncology from two angles: small molecules (chemical compounds) and large molecules (proteins and monoclonal antibodies). Then it made important acquisitions or took majority participations that boosted its research and development and turned it into the second largest biotechnology company in the world. The acquisitions were: Genentech in 1990, Boehringer-Mannheim in 1998 and the Japanese company Chugai in 2001. Says Humer, "Our alliance with Genentech probably represents our most successful move in America, and I am sure that, with time, we will see that our acquisition of Chugai will be as successful for us in Japan as Genentech was for Roche in the US. On its side, Boehringer-Mannheim reinforced our know-how of oncology diagnostics and was a key factor in acquiring access to the knowledge base of tumour markers."

Biotechnology
The pillar of growth

The combination of diagnostics and pharmaceuticals in oncology has secured Roche a powerful position in this field. "As far as I know, our approach is unique," says Humer. "In our research centre in Germany, diagnostics and pharmaceutical research in oncology are located in the same building, in order to strengthen collaboration between the two." This approach has resulted in a rich harvest of drugs for Roche. Indeed, the

"One should never forget that injecting is a dreadful act – it makes a patient sick"

company's revenue growth has been driven by its oncology division, whose 2003 sales rose 30% and accounted for a staggering 31% of its pharmaceutical sales.

This year may well turn out to be a watershed year for Roche's oncology division. In Spring 2004, a phase III study of MabThera (rituximab), a monoclonal antibody, reached its primary endpoints of response rate and progression-free survival two years early in the relapsed indolent form of non-Hodgkin's lymphoma. In February 2004, the FDA approved Avastin (bevacizumab), the first angiogenesis inhibitor for the treatment of colorectal cancer. Most recently, at the meeting of the American Society of Clinical Oncology in June, Roche unveiled encouraging results of clinical trials into two of its products: Tarceva (erlotinib), an EGFR inhibitor for use in patients with advanced non-small cell lung cancer who have progressed after standard chemotherapy, and Xeloda (capecitabine) an oral form of chemotherapy used in the treatment of colorectal cancer.

The strength of Roche's in-house R&D is reflected in 119 research projects and 61 new molecular entities – nineteen of which are in oncology and focus on solid tumours and bone metastases. It is therefore no surprise that oncology is Roche's most important R&D field, and that it absorbs close to 20% of all investments into the various therapeutic areas of Roche's Pharma division.

Humer is pleased with the success of Avastin, which he says has enjoyed a very rapid and strong uptake in the US. Roche has now filed for approval in Europe, which it hopes will be accorded by the end of the year, after which it will launch a large number of trials in several countries. Roche and Genentech have already

initiated an extensive further development programme for Avastin in order to test the drug in combination with other treatments and also to see how it works in additional indications. "We want to assess as quickly as possible where else this drug can be useful," says Humer.

With such assets, Humer sees no interest in any future merger, particularly with Novartis, its cross-town rival, which is also active in oncology: "We are not anti-Novartis. We simply oppose mergers in general. A merger does not make good industrial sense and would harm our capability to innovate. Mergers destroy teams, knowledge and research continuity."

From IV to oral drugs

Humer ranks the development of oral forms of chemotherapy for cancer patients as one of Roche's most significant achievements. Having lost his wife to breast cancer after a three-year struggle, he has a personal understanding of the plight of cancer patients. "I went through all the hopes and despairs one can imagine. I used to inject my wife with chemotherapy and, believe me, it was a nightmare. One should never forget that injecting is a dreadful act – it makes a patient sick, not to mention the fact of feeling even sicker because of being hospitalised or immobilised at home." Oral drugs, says Humer, will "change the way cancer treatment is experienced."

For the possibilities of oral drugs to be fully realised, however, Humer believes a change in the economic incentives for hospitals and physicians is needed. "In many countries, the rules of the game today in terms of financial incentives are such that if doctors or hospitals can choose between making more money on an injectable drug or prescribing an oral cancer drug, they choose the injectable one – even if the oral form is available. The incentive system needs to be restructured. We fought a two-year battle in the US to put Xeloda on equal footing with IVs in terms of reimbursement. The need is there and this is an example of an area where we can work with patient organisations." Together with Genentech, Roche is now trying to develop an orally active compound against the HER-2 target.

Relating to patients

Humer believes his personal experience of cancer alongside his wife has given him some insight into the needs of cancer patients. "The loneliness of cancer patients is not sufficiently understood," he stresses. Humer wants to see closer co-operation between patient organisations and the pharmaceutical industry, but notes: "this relationship has to be carefully structured and nurtured. It must not be a mere commercial relationship. Nor would I advocate the involvement of patient organisations in the development process, because this is driven by scientific data and regulatory requirements. On the other hand, in later stages of the development process, that is, in phases IIIb and IV, we are involving patients to a great degree and this is proving very fruitful. I favour seeing Europe move closer to the US in enabling greater access to patients."

As a step in this direction, he has appointed a go-between to enhance contacts with cancer patient organisations at the international level, with further staff responsible for liaising with cancer patient organisations in each of the major markets.

Humer is convinced that patient organisations will play an increasingly pivotal role, particularly in funding issues: "Governments won't be able to do everything and will need help in setting priorities. This is where patient organisations will have substantial influence."

Stemming the decline in European research

As the new President of the European Federation of Pharmaceutical Industries and Associations (EFPIA), Humer has set himself the mission of helping to resolve Europe's research crisis. In the last 12 years, the European pharmaceutical

"We need to change the situation dramatically if we wish to restore Europe's attractiveness"

industry has forfeited its place to the US as the world leader in sales and research. While, just a decade ago, European pharmaceutical companies invested 70% of their R&D budgets in Europe, this figure has now fallen to 50% and is expected to continue falling. Among other factors, Humer attributes the change to the faster access to markets and patients enjoyed by US companies. He believes the key to resolving the crisis lies with the recommendations of the G-10 group, established by the European Commission and made up of health and trade representatives, pharmaceutical and generic industries and patient groups.

The crucial issue is whether individual Member States will have the political will to implement the recommendations. Warns Humer: "If we don't turn this around, Europe will not have a productive pharmaceutical industry in the future, and this will be a tragedy." The new drug legislation recently passed by the European Parliament is, he notes, a step in the right direction and will accelerate the approval process: "This is particularly important in oncology, where patients often face access delays for innovative drugs. For our part, we intend to tackle access delays by putting cancer drugs on the market as soon as they receive approval, at a price fixed by us, and only afterwards begin negotiating the reimbursement price with the regulatory agencies of each country."

On the down side, Humer raises the alarm regarding the EU's new pharma legislation and clinical trials directives: "This adds another unnecessary layer of requirements. Large companies will be able to absorb this, but it will have a negative impact on smaller companies and on hospitals and research institutes.

This is the reason why the G-10 is just the beginning of our struggle. We need to change the situation dramatically if we wish to restore Europe's attractiveness."

Bob Pinedo: Bringing two worlds together

➜ Interview by Anna Wagstaff

At the tender age of 29, Dr Pinedo found himself in charge of a group of cancer patients who were being left to die, and he set out to find a way to treat them. What followed was a remarkable story of one man and his lab, whose pioneering work brought new hope to a generation of patients and helped set the standards for translational research.

Your involvement with cancer started at a time when medical oncology was not even recognised as a specialist area of medicine and all the action was taking place in the US. What prompted your interest?

BOB PINEDO It all started when, fresh out of medical school, I arrived in Utrecht to take the post of Chief Registrar in Internal Medicine. I was struck by the fact that some cancer patients were left lying on the ward, neglected and lacking treatment. They were simply dying. I was 29 at the time. I had completed my training in internal medicine in Leiden, and had just defended my thesis on hypertension. When I arrived in Utrecht, hypertension was well taken care of but cancer patients were completely neglected, so I decided to forget about hypertension, and concentrate on cancer.

What did you do?

BOB PINEDO One of the first things I did was to create a division of Medical Oncology – the first in the country and one of the first in Europe. Then I signed up for some of the general oncology courses run by the UICC [International Union Against Cancer]. In those days, Gianni Bonadonna had just started his adriamycin trials in Milan, and I introduced the drug to treat breast cancer patients in Holland. My colleagues were all highly critical. They said: "This is a terrible drug; you will give your patients heart failure." So I put my patients on a heart monitor. It seems ridiculous now, but at the time it was needed to stem the criticism and enable me to continue treatment with the drug.

By 1974, I knew I needed more training and decided to go to the US. So at the World Cancer Congress in Florence that year, I searched out Paul Carbone – who was very influential within the National Cancer Institute [NCI] – and asked if I could come over. He agreed, but when I arrived at the NCI, I was told he had just left, and true enough, his luggage was standing in the corridor. So there I was, a young man, who had come to train but had no sponsor. The staff, however, were very nice and told me: "You can do whatever you want – go ahead." So I did.

I was intrigued by methotrexate at the time, so I went to see Bruce Chabner, chief of the Pharmacology section, who was particularly known at that time for his work on this new drug. I explained that I wanted to study the pharmacology of methotrexate in mice, and he said "OK". Along the same corridor I found a basic pharmacologist, Dr Zaharko, who agreed to let me do the research in his lab. He told me about a company that had started making infusion systems that could administer drugs under the skin of mice, and suggested I write a protocol. I proceeded to do it and it won his approval. Then I had to do the pharmacology. So I went back to Chabner's lab and asked the assistant technician there to show me how to measure mouse methotrexate levels. I began the research and it proved a big success. But I also needed to study the effects on bone marrow stem cells, so I set out to find a lab where they had bone marrow stem cells I could use to culture my mouse marrow. I found Dr Joan Bull, who had previously been working with Carbone, and she said: "Fine, go ahead." This was what was so nice there. Though the person who had brought me to the NCI had left, everyone was eager to give me a chance. Eighteen months later I had already five papers published in *Cancer Research* and other leading US journals on the effects of methotrexate on the bone marrow of mice. That, for me, was the real scientific start.

How did you use the knowledge you gained at the NCI to improve the treatment of your patients back in Utrecht?

BOB PINEDO Apart from my contribution towards researching methotrexate, I learned at the NCI about how the skills of a basic scientist could be combined with my training as a clinician to better understand what effect a particular dosage of a particular drug and metabolism has on a particular patient. I was determined to set up a

Two years later, my critics all started using the drug themselves

With Bruce Chabner. "Pinedo and Chabner" became known to generations of oncology students through the *Cancer Chemotherapy* annuals they edited for many years. The two of them became lifelong friends during Pinedo's days at the NCI, where Chabner was Chief of Pharmacology

Most of the cancer drugs came from Europe, because the European chemists are good

lab when I returned to Utrecht, and combining the worlds of scientist and clinician has been my approach to patient care ever since.

Shortly before I left the US, in 1976, Chabner told me of an experimental pharmacologist named Al Leyva who had just applied for a job at the NCI. So I called him and said: "Al, can you help me? I am a clinician and I want to set up a lab." He agreed to help, and a few weeks later we set up the lab at the hospital in Utrecht, and started doing pharmacology in patients, beginning with high-dose methotrexate for osteosarcomas. We created quite a stir and came in for a lot of criticism.

Was there no regulation limiting your freedom to experiment in this way?

BOB PINEDO No. One could just go ahead. For instance, we didn't have the money to pay for the methotrexate we needed, so I asked Al to purify it from the patient's urine, because almost 90% of this expensive drug is excreted in the urine. So we purified it and gave it back to the patient. This worked fine. I still see one of those early patients.

After that, we started trying out platinum on testicular cancer. I knew that Larry Einhorn, whom I had met in the States, had achieved terrific results with platinum, but the drug had never been used in Europe. So when a colleague of mine developed testicular cancer we agreed I should pick up some platinum on my next trip to the US, which I did and brought it back in my pocket.

Then I began receiving phone calls from oncologists in our Cancer Institute: "Are you crazy to use platinum? You will make these patients horribly sick." It was true. My patient was very sick. He was the first patient in the Netherlands – probably the first in Europe – to be given platinum, and we were still learning how to use the drug properly. But he survived, and his metastasis disappeared. And he still visits me every year. Two years later, my critics started using the drug themselves. This is how I had to do things, because if I'd done it in another way, it would have taken years.

After that first patient, we drew up a protocol for a proper trial of platinum in testicular cancer, and then went out to many hospitals and presented our first ten cases. We explained that we wanted to learn how to use the drug, and people were impressed and started referring patients to us. A few years later, I and Dr Stoter (who was a member of my staff, and is now professor in the Rotterdam Cancer Institute), published an important paper in the *Lancet* showing very good results. We then moved on to using a platinum regimen in ovarian cancer, and again we conducted a large study in Holland, known as the Dutch Ovarian Cancer Group. This was within a couple of years of returning from the NCI, and there were still only four of us doing this work.

You achieved all this by the age of 35 with very little money and no co-operation from those around you. How do you account for the fact that today we see such slow progress from million-dollar research efforts and huge multi-centre collaborations that were unimaginable in your early days?

BOB PINEDO It's not the money that determines the result, it's the method. Let us not forget that while the big research money and major trials are concentrated in the US, most cancer drugs come from Europe, because European chemists are good. Adriamycin came from Italy, carboplatin from the UK, VP16 from Switzerland, oxaliplatin from France, cyclophosphamide from Germany, and now CPT 11 for colon cancer, also from France. The US has the system and the money. They are good at taking a European drug and doing big trials.

When it comes to translational research, the number of participating centres should be limited.

With Frits Duparc, Director of the Mauritshuis art museum in the Hague, at an oncology Masterclass in Tenerife last year. Duparc was one of three patients Pinedo invited to talk to the young doctors on the course about how patients feel about discussing their disease

If we don't think about the pharmacology of drugs we can cause a lot of harm to our patients

Take adriamycin. It was developed here in Europe by Gianni Bonadonna at his own institute. He said: I don't want to involve the EORTC [European Organisation for Research and Treatment of Cancer], I have enough patients in my institute. And it was a hit.

Translational research makes use of the tissues and blood of your patients to understand the biology in the patient, the pharmacology, and pharmacodynamics. This involves not only measuring the drugs, but measuring the effects of the drugs on organs. It is meticulous work and the most important thing is to achieve complete standardisation of the processing of the tissue and close observation of the patient. This is much harder to achieve when several centres are involved.

In my view, the European Community is making a mistake in always seeking collaboration between many groups – eight or twelve centres in four or five countries. That is good for trials, and it may be good for basic scientists, but for translational research, 4x2 is better than 1x8. So please, European Community, accept small groups. We can each do an excellent job in our area, and have standard tissue processing.

Translational research is strongly promoted by large sections of the cancer world today, but how much is it actually taught to trainee clinicians and basic scientists?

BOB PINEDO When I joined the Free University, Amsterdam, in 1979, as Professor of Medical Oncology and Head of the newly created Department of Medical Oncology, I made it my priority to teach my students the philosophy of

But just sitting in that coffee room and listening to what the nurses are saying is crucial

translational research and the importance of bringing the worlds of scientists and clinicians together. Unfortunately, this is not generally the case elsewhere. We held regular clinical research seminars attended by basic scientists, where the presentation was oriented towards patients, not science. And we held basic science seminars attended by clinicians, which were oriented towards basic science. Basic scientists were encouraged to come with clinical proposals, make suggestions, and ask the clinicians all sorts of stupid questions. And clinicians were encouraged to feel free to ask the basic scientists stupid questions of their own. This broke the ice.

I also insisted that the clinicians pursue a lab project, and that the basic scientists spend one week in the clinic, on the unit, with the nurses, residents and interns. Can you imagine a chemist or a biologist involved in a phase I trial sitting and listening to clinicians explaining the proposition to patients, talking through the patients' concerns and maybe hearing patients explain why they don't want to participate?

Initially I met with a lot of resistance. It's strange for a biologist to sit and drink coffee with nurses and listen to them discussing the problems of this or that patient. But just sitting in that coffee room for half an hour and listening to what the nurses are saying is crucial. At the simplest level, it helps them understand why the piece of tissue they need to examine arrives at 5.30 in the evening, and not at 8.00 in the morning, because the surgeons who have to take that biopsy for the protocol for the translational research won't do it in their routine programme. They will do it at the end of their programme, at around 3.00 or 4.00 in the afternoon. That is why you may have to stay an hour or two longer in the lab to process the tissue. And if you have been in that environment for a week, you understand this, and you feel more motivated because you see the two worlds coming together.

I also think it's very important for medical oncologists to know internal medicine and understand the pharmacology of the drugs they prescribe. The problems of our patients affect all organ systems – we have to deal with cardiac toxicity, renal toxicity and so on. Many of our patients will have comorbid conditions and will need other drugs as well, and the functions of their organs are often abnormal. Medical oncologists need to ask the question: "What is happening with the painkiller I prescribed if the liver is not functioning well?" If we don't think about the pharmacology of drugs we can cause a lot of harm to our patients. This is not taught enough in medical schools.

Breaking down barriers between the world of the patient and the world of the clinician is something that is also very important to you.

BOB PINEDO I can tell my patients everything and they can tell me everything. A newly-diagnosed may tell me she wants to postpone the start of her treatment. So we sit down and talk frankly about the risks of waiting, say, until after her holiday.

All drugs are very important, but half of the work is how you approach your patient, and I'm convinced that an empathic approach helps them live longer. I have a patient with a tumour on her liver, who enjoys biking. Every time I palpate that big protruding liver, I know she will be watching the expression on my face. I can either grimace, and utter – "Oh God!" – or I can ask her: "How far have you biked today?" And we will talk about the good things in her life. This is the secret of homeopaths. They make use of the shortage of doctors, and take time with their patients – time that we don't have. The patients are happy and I believe live longer as a result. This particular patient has been biking around with a huge liver for four years, after having been told she would die in three months.

How do you teach this approach to your students?

BOB PINEDO By doing rounds. On teaching rounds, the students follow you around and they see how you talk with your patients and how you touch your patients. Touching your patients is not taught in medical schools, but most patients like to be touched if you are talking to them. Not necessarily Spanish-style, when you kiss your patients on both cheeks – though I do have Spanish patients, and I am happy to greet them in this way. I also have many patients from Curacao, which is where I come from, and when I see them on my rounds I will say two or three words in Papiamentu. None of my students understand, but the patients are delighted. You need to find a connection.

I also teach Masterclass courses for the European School of Oncology, where I have the chance to talk to medical oncologists from all over Europe, including many countries where there is very little tradition of openness with patients. I recently invited three of my patients to accompany me on one of these courses so the doctors at the Masterclass could see how I talk to them, and how they talk to me. I wanted to let them speak – to say how they feel about discussing their cancer, what they feel about phase I trials, or what they feel about anything. They did a wonderful job. They could see some of the doctors were afraid to ask questions, so one of my patients said: "Listen, I want you to ask me anything that comes to mind. I can talk about it, I know I am going to die."

Many of the doctors were shocked and didn't know how to respond. If we keep doing this, particularly at international courses, I believe we will get the message across.

Where do you see progress in the fight against cancer being made?

BOB PINEDO I think targeted agents will be very important, and a much better multidisciplinary approach. We need to start talking more about surviving with cancer and not only stressing the cure. Many people are failing to recognise how much longer our patients are living now than they did 25 years ago. Instead of three months, they live eight years. I am convinced that cancer will become a chronic disease, as long as we have enough doctors and enough time for our own patients. We need to start getting people accustomed to this.

Some of my patients are reluctant to go to work because people tell them they "stink of chemotherapy" – this can be a terrible blow to a person who is fighting cancer. Businesses must learn to accept the fact that they have four or five cancer patients in their office, and the whole social system should be more accommodating to patients living with cancer. We should stop talking just in terms of a cure rate, because the time is coming when these targeting agents, even if they don't eliminate cancer, will keep it under control and society will have to make the necessary adjustments.

The human touch

Start talking more about surviving with cancer and not only stressing the cure

EBCC: Driving up standards in breast care

Peter McIntyre

The European Breast Cancer Conference set up by researchers, clinicians and advocates who wanted to co-ordinate their work and widen the fight against cancer to include the public and politicians. This year it took place under the shadow of the Clinical Trials Directive.

In 1998, three of Europe's leading organisations representing researchers, clinicians and women cancer advocates launched the biennial European Breast Cancer Conference (EBCC) to co-ordinate breast cancer research, educate primary care providers about breast cancer and sensitise politicians and women to the potential for progress.

These conferences are unusual in that they bring together, on an equal footing, researchers, clinical practitioners and women activists, and are oriented as much towards the public and politicians as towards professionals. Each EBCC issues a closing statement, which makes demands on national politicians, the EU and on clinicians and researchers.

They press for measures to improve the legal framework for research and treatment, the interchange between research and clinical practice and the management of services. They push ethical issues up the agenda, and introduce the patient view into debates.

The statements emanating from the biennial conferences carry great weight because of the authority of its three organising bodies:

- The Breast Cancer Co-operative Group of the European Organisation for Research and Treatment of Cancer (EORTC) – an important driver of laboratory and clinical research in Europe.
- EUSOMA (the European Society of Mastology) – the organisation that sets standards in the management of breast diseases, and helps clinicians and centres to meet the standards to become specialist breast units.
- Europa Donna – the coalition of breast cancer groups throughout Europe that represents the concerns and interests of women.

Both EORTC and EUSOMA promote translational research, seeking to move laboratory discoveries quickly into clinical trials and to minimise the delay between the development of effective anti-cancer therapies and their use in patient treatment.

Europa Donna has proved a powerful lobby, pressing authorities and governments for improvements. It played a key role in securing a strong resolution in the European Parliament, in June 2003, aimed at reducing cancer mortality by 25% across Europe – the first policy ever passed by that body on a specific disease.

The EBCC formula emerged from lengthy discussions in the early 1990s around the possibility of

extending the former EORTC Breast Cancer Working Conference.
The plans were finalised in June 1995, at a meeting hosted by Umberto Veronesi and attended by representatives of the three organising groups and the Federation of European Cancer Societies. It was a success from the first and has since grown in size and diversity. In 1998, Florence attracted more than 3,000 delegates from 74 countries. The fourth EBCC in Hamburg this year welcomed 3,599 delegates from 82 countries.

Focus on optimal care

Florence focused on the quality of treatment, demanding that all women should have access to multidisciplinary and multi-professional breast clinics. It also drew attention to the need for research to feed more quickly into clinical trials and treatments. By the time of the second EBCC in Brussels in 2000, the three societies had agreed guidelines defining the requirements for these dedicated breast units. The Brussels Statement called for all breast units to develop quality assurance programmes and to contribute to a common European database. It also called for mammogram screening to be implemented throughout Europe for women aged between 50 and 75, free at the point of delivery. The statement expressed early concerns about the future of European research projects. The Brussels Statement called for informed consent to be routinely obtained from all breast cancer patients for the use of frozen tumour specimens. However, the EU, driven in part by public disquiet about medical abuses, was pursuing a different agenda.

Research concerns top the agenda

Fast forward two years to Barcelona in 2002, and the third EBCC recognised "pan-European concern about the future of clinical and translational research for cancer in general and breast cancer in particular". The conference was presented with data about the steep increase in age-specific mortality from breast cancer between the war and the mid 1980s, followed by a significant fall in mortality between 1987 and 2000.
There was a consensus that around two-thirds of the reduction in breast cancer mortality could be attributed to improvements in treatment since the first trials of tamoxifen in older women and cytotoxic chemotherapy for pre-menopausal women.
The Barcelona Statement feared that European multi-centre trials, which were largely responsible for continuous incremental improvements in treatment, were under threat by "well meaning, but

Since its founding conference in Florence, 1998, the EBCC has gone from strength to strength. This year's gathering in Hamburg was attended by more than 3500 delegates from 82 countries

The 4th EBCC, in Hamburg, was chaired by Jacek Jassem, the dynamic head of Oncology and Radiotherapy at the Medical University of Gdansk. He is pictured here at the opening ceremony

misguided, bureaucratic challenges". Indeed, what the EU called 'good clinical practice' as applied to clinical trials, patient confidentiality and ethical issues would make trials difficult to conduct and prohibitively expensive.

Ethics Committees were tightening their interpretation of the Helsinki Declaration on ethical research to the point of threatening the recruitment of patients into trials. The statement said that unless Ethics Committees encouraged cancer research they would become obstacles to progress, "carrying equal responsibility for unnecessary loss of life in the future, as those clinical scientists who have abused the trust of the public in the past".

And so to the fourth conference in Hamburg in March this year, barely a month before the European Directive on Clinical Trials came into force. The Hamburg Statement – published in full on these pages – issued a clear warning: "Excessively rigid legislation, unjustifiable administrative restrictions and government budget cuts are threatening cancer research in general, and breast cancer research in particular." The EU directive was said to be especially damaging to research into surgery, imaging, radiation therapy and tailoring treatments.

There were calls for action. Karin Jöns, the European Parliament's standing rapporteur for breast cancer, who is herself a breast cancer survivor and President of the German Forum of Europa Donna, criticised the fact that only eight European countries currently offer nationwide mammography screening, and many of these are not in line with EU guidelines.

The need for screening was underlined by a controversy over self-examination. Professor Lars Holmberg, from the Uppsala Regional Oncologic Centre, Sweden, said that self-examination raised anxiety levels to no good effect and could be positively harmful.

He based his remarks on a Russian study, which found that women were reporting more benign lesions to their doctors without any reduction in cancer deaths.

Focus on age

Age-related issues were a recurring theme. The Institut Gustave Roussy in Villejuif, France, reported that women who carry the highly aggressive BRCA breast cancer gene are at no greater risk of relapse after treatment. The gene is associated with cancer in young women, who are prone to recurrence. However, the risk factor appears to be age, rather than genetics.

Dr Suzette Delaloge, assistant professor at the Institut, called for more research into why younger women relapse. Younger women who survive breast cancer can suffer long-term physical and psychologi-

cal after-effects. Dr Lonneke van de Poll-Franse from the Comprehensive Cancer Centre South in Eindhoven, in The Netherlands, said that 22% of younger women were having problems with unusual tiredness even ten years later, compared with only 4% of older women.

In general, follow-up care is not reassuring. Ingrid Kössler, President of the Swedish Association of Breast Cancer Societies, reported on a questionnaire returned by 600 women following treatment for breast cancer, which revealed that follow-up examinations were often hurried, with no opportunity to ask questions, express emotional concerns or talk about a woman's social situation.

She called for research into follow-up by specialist nurses.

It is not only young women who need special attention, but also the elderly. Professor Holmberg said that doctors were not trying hard enough to find suitable treatments for women aged 75 or older, who make up a quarter of breast cancer patients and who have a worse prognosis than younger patients.

The consensus session, chaired by Alberto Costa, where delegates vote on which issues to prioritise in the closing statement

"We don't know enough about attitudes among physicians; we don't ask elderly patients what they want; and we don't do enough specific trials for them."

Professor Silvio Monfardini, from the Division of Medical Oncology, Padova, Italy, agreed on the need for trials. "If this is not done we will discriminate against an already vulnerable group and deny us information on a very relevant part of the breast cancer population in Europe."

Targeting treatment on specific age groups is a step towards individual packages of care, which is the direction signposted by research. Dr Alane Koki, Chief Scientific Officer of the French biotechnology company, Ipsogen, said that significant progress was being made towards identifying the genetic make-up of individual tumours, allowing treatment choices that are based on personalised information.

Ipsogen has developed a breast cancer profile chip for use in local pathology laboratories.

Widening the fight

The next EBCC, in Nice in 2006, will be chaired by Alberto Costa, a breast surgeon from Pavia, Italy, and Director of the Milan-based European School of Oncology. At previous EBCCs he moderated the drafting sessions that developed the influential conference statements.

Dr Costa has a number of plans for Nice. He will invite experienced breast care nurses, to spread the concept of specialist breast care nursing beyond Northern Europe.

Dr Costa also hopes that some of the big cancer charities in Europe will attend, creating a forum for discussion on how to fund multi-centre, multi-national trials on breast cancer at a European level.

He said: "If we can include some of the major cancer charities in the Nice EBCC, it will strengthen links between those who raise money and the researchers and clinicians who need the funding to target treatment more precisely. If this led towards some national cancer charities combining resources to fund a major European cancer trial, that would be a fantastic step forward."

The Florence, Brussels and Barcelona Statements can be found on the Eusoma web site at www.eusoma.org
(go to Guidelines and Publications, EUSOMA Statements)

The Hamburg Statement

The partnership driving the European agenda on breast cancer

Breast cancer is the commonest cancer and the most frequent cause of cancer death in women throughout Europe. However, mortality from breast cancer is decreasing as a result of concerted action by all parties involved (women at risk, doctors, nurses, researchers, patients, journalists etc.). Partnership is paying off. Increasing numbers of breast cancer patients may nowadays achieve a normal life expectancy.

All previous European Breast Cancer Conferences produced Statements that became important tools in communicating with politicians and the media and we want to continue building upon this successful approach. Previous statements (Florence, Brussels and Barcelona) addressed the importance of screening programmes, translational research, patient involvement, risk assessment and the need for breast cancer to be managed in multidisciplinary clinics (breast units) according to the guidelines recently approved by the European Parliament. The 4th European Breast Cancer Conference in Hamburg reached a consensus on key issues during the closing plenary session on the 20th March 2004. Clinicians, scientists, advocates and health care consumers representing 3,599 participants used a computerised voting system to formulate the Hamburg Statement.

The delegates of the 4th European Breast Cancer Conference wish to give priority to the following four areas:

Academic research

Excessively rigid legislation, unjustifiable administrative restrictions and government budget cuts are threatening cancer research in general, and breast cancer research in particular. In addition, the new European Directive on clinical trials might exacerbate this by leaving cancer research almost entirely to the initiative of the pharmaceutical industry. Whilst not denying the contribution of those pharmaceutical companies engaged in new drug development, the participants in the 4th European Breast Cancer Conference are concerned that this situation will lead to a decline of non-pharmacological research (in surgery, imaging, radiation therapy, treatment tailoring etc.). This negative effect on independent academic research will also encourage even more gifted European researchers to emigrate to the United States to complete their studies and projects.

Participants in the 4th European Breast Cancer Conference call for a more determined financial and structural support to academic research, facilitation of the free circulation of tissue and blood samples within the European Union for research purposes, and a greater involvement of patients and consumers in research planning and monitoring. They also propose that funds originating from the EU central budget (e.g. a percentage of the current annual tobacco subsidy) are re-allocated to transnational research on breast cancer and also that private donations to breast cancer research are encouraged through the raising of the tax deductibility level currently imposed on such contributions in all Member States.

Individual risk assessment

Women increasingly want to know about their individual risk of developing breast cancer. All breast units should put in place special clinics for the assessment of individual risk and develop research in the field. Counselling should include a discussion of all proven risk-reducing measures, their availability within the relevant healthcare system and assistance in privacy protection. As risk-reducing interventions are being developed the issue of their availability, at no cost to the patient, should be addressed.

For women with a serious family history of breast cancer full genetic counselling should be offered and be made freely available, without cost, to the patient. Genetic testing, when indicated, should also be provided at no cost to the patient.

Age limits

Most diagnostic and treatment protocols and procedures in breast cancer have age limits, but evidence is lacking for most of these limits. The 4th European Breast Cancer Conference wishes to draw attention to the growing size of the elderly population and their special needs, and proposes that participation in clinical trials is decided according to physiological status rather than age and that no upper age limit is laid down in the design of standard prevention and treatment plans.

Care after breast cancer

The 4th European Breast Cancer Conference recognises the need to redefine the concept of care for breast cancer patients after primary treatment. Routine continuous follow-up, as currently practised, does not serve women well. Care after breast cancer should not just aim at detecting local relapse and second primary tumours but should also include psychological support and the management of treatment side effects. On the other hand, no consensus seems to exist on the duration and frequency of follow-up, nor on the schedule of requested examinations. For those patients treated outside a research setting, care after primary breast cancer treatment should be planned by the multidisciplinary team and individually tailored following discussion with the patient.

Conclusion

Breast cancer incidence is increasing, and deserves priority.

The four aspects addressed in this document – academic research, assessment of individual risk, breast cancer in the elderly and care after breast cancer – represent major issues in breast cancer management.

Research is fuelling progress, and clinical trials and translational research must be supported. Increasing knowledge of risk assessment should be translated into comprehensive individualised approaches.

Better care should be provided to elderly patients and breast cancer survivors.

The Breast Cancer Group of the European Organisation for the Research and Treatment of Cancer (EORTC-BCG) and the European Society of Mastology (EUSOMA), together with Europa Donna, the European Breast Cancer Coalition, will work towards these goals by lobbying European Governments, the European Parliament and the European Commission and by mobilising health-service providers, the scientific community and the healthcare industry. You are invited to spread this statement, and the proposals put forward in it, in order to further advance the improvements already made in breast cancer research, treatment and policy in Europe. The measures called for by EBCC-4 delegates will be reviewed at EBCC-5 to be held in Nice, France in March 2006.

The Hamburg Statement was published in the European Journal of Cancer vol. 40, pp. 1810-1811, and is available online at www.eusoma.org and www.fecs.be

Advanced head and neck cancers

Transatlantic collaboration shows results

Janet Fricker

Concurrent postoperative administration of cisplatin (Platinol) and radiotherapy has been established by two separate studies to be the treatment of choice in people with advanced head and neck cancer who have undergone surgery.

Taken together, the results of the European Organisation for Research and Treatment of Cancer (EORTC) study and the US Radiation Therapy Oncology Group (RTOG) study, both published in the May 6 issue of the *New England Journal of Medicine* (vol 350, pp 1945–1952 and 1937–1944, respectively), showed benefits from the concurrent therapies compared to radiotherapy alone. This treatment was already the established therapeutic option for tumours that had spread locally, but which were not considered operable.

But while both studies were positive – showing enhanced disease-free survival at five years in the EORTC group and enhanced two-year local and regional control in the RTOG group – only the EORTC study demonstrated significant increases in survival. "These are puzzling discrepancies, that require further investigation," said Professor Jacques Bernier, principal investigator of the EORTC study and director of the Department of Radio-Oncology at the Oncology Institute of Southern Switzerland, Bellinzona.

Squamous cell cancer of the head and neck is the sixth most common cancer worldwide, with a lifetime risk of 2% for men, and 0.6% for women. There are approximately 76,000 new cases of oral-cavity, pharyngeal and laryngeal cancer diagnosed each year in Western Europe. "Patients often have a genetic predisposition to head and neck cancer which favours malignant transformation if they come into contact with tobacco and alcohol," said Professor Bernier.

Professor Jacques Bernier, principal investigator of the EORTC trial, is keen to find an explanation for discrepancies between the results of the two trials

Early disease is generally treated with either radiotherapy or surgery, which have a similar likelihood of controlling tumours. But for patients with locally advanced disease – i.e. disease that has spread locally from its site of origin, but not to distant sites in the body – treatment is more complex, requiring surgery with postoperative radiotherapy. Unfortunately such patients still show a particularly high rate of local recurrence. When two or more regional lymph nodes are involved, or there is extra capsular spread of disease or microscopically involved mucosal margins of resection, there are particularly high rates of local recurrence (27–61%), distant metastases (18–21%) and a high risk of death, with a five-year survival rate of 27–34%, indicating the need for development of additional treatments.

Such statistics have led investigators to look at different ways of delivering chemotherapy, including induction chemotherapy (consisting of several courses of chemotherapy before radiotherapy); sequential chemotherapy (where chemotherapy is administered at a different time from radiotherapy); concurrent chemotherapy (where chemotherapy is given at the same time as radiotherapy) and adjuvant chemotherapy (administered after patients have been rendered disease free). Studies looking at delivering sequential chemotherapy postoperatively have revealed little in the way of benefit. Most noteworthy, the

Inter-group study 0034, published in the *Journal of Clinical Oncology* in 1990 (vol 8, pp 838–847), showed that the sequential addition of cisplatin and fluorouracil to radiotherapy reduced the incidence of nodal and distant failure, but produced no effect on survival.

However, other studies suggested that for patients with inoperable head and neck cancers, chemotherapy was beneficial when delivered at the same time as radiotherapy. The RTOG 88-24 study, published in 1997, which gave cisplatin in a single high dose (100mg/m^2) on days 1, 22 and 43 of radiotherapy (*Int J Radiat Oncol Biol Phys* vol 37, pp 777–782), showed improved local control and increased survival. Whilst severe toxicity occurred in 20% of cases treated with adjuvant chemo-radiation, 48% of patients remained alive at three years and 81% had locoregional control of disease.

A study published in 1996 showed benefits from combining postoperative radiotherapy with weekly cisplatin infusions for locally advanced head and neck cancers (*Int J Radiat Oncol Biol Phys*, vol 36, pp 999–1004). Another, published in 1993, found improved outcomes combining postoperative radiotherapy with Mitomycin C (*Int J Radiat Oncol Biol Phys*, vol 27, pp 241–250). In both these studies, disease-free survival was increased for patients in the combined therapy arm compared to those in the control arm, who just received radiotherapy.

This was the background against which the recently published EORTC and RTOG trials were started, in 1994 and 1995 respectively. Both were much larger than the earlier studies and both aimed to establish whether adding cisplatin concurrently to postoperative radiotherapy improved outcomes for patients with high-risk resected head and neck cancers. The focus on cisplatin was due to its presumed effect of "radiosensitising" cells – i.e. rendering cells more vulnerable to the toxic effects of radiation when administered concurrently – which was expected to yield a greater benefit than the sum of the benefits of radiotherapy and chemotherapy considered separately. (The interaction between cisplatin and ionizing radiation is not fully understood, but may be achieved by the synchronisation and redistribution of tumour cells into the more sensitive G2-M phase of the cell cycle, or by the cisplatin creating abnormal ridges within DNA that inhibits its capacity to spontaneously repair after radiotherapy.)

Protocols and patients

The EORTC trial involved patients with stage III or IV head and neck cancers. After undergoing surgery, 167 patients were randomly assigned to receive radiotherapy alone (66 Gy over a period of six weeks) and 167 to receive the same radiotherapy regimen combined with 100 mg/m^2 cisplatin on days 1,22 and 43 of the radiotherapy regimen. The study, which had a median duration of follow-up of 60 months, was designed to detect an absolute increase of 15% in disease-free survival. The RTOG trial, which followed exactly the same treatment protocol in a similar patient population, assigned 210 patients to postoperative radiotherapy and 206 to combined therapy, with a median duration of follow-up of 45.9 months. The trial was designed to detect an absolute increase of 15% in the two-year rate of local and regional control.

The eligibility criteria for the two trials differed, but overall patients had to be in good general condition to receive chemotherapy and to have a previously untreated, histologically proven squamous cell carcinoma arising from the oral cavity, oropharynx, larynx or hypopharynx. The cancer had to be classed as stage III or IV, or had to show high-risk characteristics such as histologic evidence of invasion of two or more regional lymph nodes, extracapsular extension of nodal disease or microscopically involved mucosal margins. "Cancers of the nasopharynx were excluded from the studies because it was felt they had a different natural history from the other head and neck cancers (with faster metastasis) and would skew results," said Dr Bernier. All patients had undergone surgery with curative intent and those with distant metastases were excluded from the study.

"In both studies cisplatin was selected because it was considered the best agent at the time to increase the control without increasing the toxicity", said Dr Bernier. "Although 5-FU, for example, is very effective, it has the disadvantage of increasing mucosal reactivity to radiotherapy and can result in patients needing parental feeding and severely adverse effects on quality of life."

Positive results

Both studies yielded positive results. In the EORTC trial, after an average of approximately five years, progression-free survival was 47% in the group of patients treated with cisplatin plus radiation, compared with only 36% in the group of patients treated with radiation alone. The overall survival rates at five years were 53% for patients treated with cisplatin and radiation therapy, compared with only 40% for patients treated with radiation alone. Severe side effects (grade 3 or higher) occurred in 41% of patients treated with combination therapy, compared with only 21% of patients treated with radiation alone. But severe mucosal adverse effects were similar in the two groups.

In the RTOG trial, after approximately 46 months cancer-free survival was 22% higher in the patients treated with radiation and chemotherapy, compared

to those treated with radiation alone. However, overall survival was similar. Cancer recurrences at or near the site of origin occurred in 18% of patients treated with combined therapy, compared to 28% of patients treated with radiation alone at approximately two years following treatment. Severe side-effects occurred in 34% of patients treated with radiation alone, compared with 77% of patients treated with chemotherapy and radiation therapy, and in this study four patient deaths were directly attributable to treatment.

"The magnitude of a 13–15% difference in survival observed in the EORTC trial was both much higher than the RTOG trial and higher than we'd been expecting, suggesting there are additional mechanisms in play that we've yet to determine," said Dr Bernier, who wants to find out why the beneficial effect was so much higher than in the RTOG trial. Differences in the presentation of morbidity data make comparisons of the two trials difficult. There are, however, suggestions that differences in overall survival found between the two trials might be attributable to differences in the types of patients recruited to each study, since they did not use identical eligibility criteria.

Another theory, put forward by Dr Jay S. Cooper, principal investigator of the RTOG trial and head of Radiation Oncology at Maimonides Medical Center in New York City, is that over time an effect on overall survival may still be seen in the RTOG trial. "If you don't find a mathematically statistically significant change, it doesn't mean one doesn't exist," he said. It is also possible, he suggests, that certain lifestyle issues that contributed to the cancer (such as heavy drinking and smoking) caused other problems, such as heart disease. "Even if you do a better job of controlling tumours, it may not translate immediately into better survival, because they'll still die of other things," he said.

Investigators from EORTC and RTOG hoped to review differences between the two trials when they met at the Sixth International Conference on Head and Neck Cancer in August. "We plan to screen for variations in patient selection and treatment density across the two trials to see if these could account for the differences in magnitude," said Dr Bernier.

Despite the positive findings, neither trial showed any reductions in distant metastases, and disease still recurred locally in 30% of patients, demonstrating that further improvements are still needed. One way forward, suggested Dr Bernier, may be to give chemotherapy immediately after surgery. "We'd keep the chemo as used in this study, but also give a weekly cycle of chemotherapy seven to ten days after surgery until the beginning of radiotherapy."

Toxicity concerns

Issues remain concerning toxicity, and future clinical trials evaluating agents not associated with such a high rate of side-effects are warranted. One novel targeted therapeutic approach under investigation is the agent Erbitux (cetuximab), which is a monoclonal antibody designed to bind to EGFR, a protein involved in the growth and replication of cells that is often over-expressed in cancer cells.

This binding action is believed to prevent or reduce the replication of the cancer cells, resulting in anti-cancer responses. In a trial presented by the Erbitux Head and Neck Study Group at the 40th Annual Meeting of the American Society of Clinical Oncology in June, 417 patients with locally advanced head and neck cancer were randomised to receive Erbitux plus high-dose radiation, or high-dose radiation alone (Abstract 5507). Three-year overall survival was 57% for patients treated with Erbitux plus radiation, compared with only 44% for those treated with radiation alone. The median survival increased from 28 months in the standard arm to 54 months in the experimental group. The only notable side-effect associated with Erbitux was skin rash.

Next steps

Advances are also needed in radiotherapy. In an editorial which appeared in the May issue of the *New England Journal of Medicine*, alongside the EORTC and RTOG trial results (vol 350, pp 1997–1998), Michele Saunders, from the Academic Department of Oncology at University College London, and Ana Rojas, from Mount Vernon Hospital, Middlesex, UK, suggest that the next obvious step towards further improving outcomes would be to identify a more effective radiotherapy regimen. "The radiobiology of radiotherapy as the sole agent in the treatment of squamous cell cancer of the head and neck is well understood, but the optimal dose, time frame and regimen of fractionation in a multidisciplinary setting are not." Two recent phase III trials indicate that use of a shorter than conventional overall treatment time for post-operative radiotherapy could improve tumour control and survival.

Dr Bernier believes the two studies make a convincing case for the standard use of the concurrent combined therapy, at least in the age group 70 and under. "This transatlantic collaboration justifies the fact that most countries now consider the combination of high doses of cisplatin and radiotherapy to be the new algorithm in the decision making process for locally advanced head and neck carcinomas treated with primary surgery," he said.

Nothing about us without us

Europe's patient advocates gather for the first time

Anna Wagstaff

From every corner of Europe and beyond, they descended on Milan. Patients and former patients with breast cancer, leukaemia, prostate and testicular cancers, multiple myelomas or lung cancer. Some were experienced cancer advocates and campaigners, others were active in support groups, or were in the first stages of setting up a patient association. Yet others, from countries with no history of patient organisation, came as individuals. All had one purpose in mind: to assert the voice of the patient in all decisions that might affect them, in order to improve the outlook for all cancer patients.

This was the first meeting of the European Cancer Patient Coalition (ECPC), held at the European Institute of Oncology in Milan, June 12-13. Billed as a Masterclass in Patient Advocacy, it was designed to equip delegates with the information they need to campaign effectively for an end to needless suffering. Cancer patients suffer when they don't have the information they need at the right time, when their disease is picked up too late or when they are treated inappropriately by medical staff with too little specialist experience. Even as survivors, their quality of life is often blighted by a lack of understanding and support.

Using the European School of Oncology's official language ('bad English'), a procession of experienced patient activists, politicians, and medical and research professionals filled in this international gathering on everything they might ever need to know. This stretched from the details of Europe's complex democratic, bureaucratic, legal, regulatory and consultative structures to advice on dealing with politicians and the media. There was also a focus on reaching out to other patients, working in alliance with one another, with disability groups, and with the medical profession and drugs industry.

Perhaps most valued by the delegates were opportunities, during coffee breaks and meal times, to swap anecdotes and contact details and to network: "Everyone I went to sit next to had something I could learn from," said Lia van Ginneken-Noordman, from the Multiple Myeloma and Waldenström Macroglobulinemia Patients Association in the Netherlands (CKP), after a busy evening chair-swapping at the formal dinner. ECPC Chairman Lynn Faulds Wood said: "Our first Masterclass in Cancer Patient Advocacy was an incredible experience. Over 100 cancer patients organisations were represented, from 33 countries, and every session was packed – no one seemed to want to leave the meeting to take a look at Milan! ECPC aims to be a sort of 'virtual trade union' of cancer patients, sharing ideas and best practice to help reduce inequalities within countries and across Europe, to improve access to good treatment for all.

"We are a potent force and together we can help to change our world: our mantra – 'Nothing About Us, Without Us!' – is becoming a reality."

The personal and the political

Two former Health Ministers, Italy's Umberto Veronesi and Holland's Else Borst-Eilers, contributed to a round table discussion on politics and cancer. They agreed that access to top quality treatment and screening remains shockingly unequal between and even within the countries of Europe. However, they said that politicians face pressures from many directions, and while they will always sound sympathetic behind closed doors, you must use every weapon at your disposal if you want to see real change. Public campaigns in the Netherlands helped to slash waiting lists, and in the UK gave chronic myeloid leukaemia (CML) patients access to the drugs they need free of charge. Taking test cases through the courts has also proved effective, for instance, in establishing the obligation of national health systems to pay for treatment abroad, if the patient cannot get the treatment he or she has a right to expect in their own country.

Stella Kyriakides, President of Europa Donna – The European Breast Cancer Coalition – told the story of the long campaign that led to an important breakthrough on breast cancer policy at the European Parliament. Patient advocates, she said, are uniquely powerful; they take painful personal life events and put them to use in driving political change. Speaking from the floor, Rita Rosa Martin, from the German breast cancer organisation Breast Health, argued that if national governments and European institutions want to consult and involve patients groups, then they must provide funds so that groups can buy in equipment and training to play an effective role. "I for one," she said, "am no longer prepared to be grateful simply for being asked for my opinion or advice." The example of the Netherlands, where lobbying led to 30 million euro of state funds being made available annually to patient groups, was held up as a possible lead for ECPC and national groups to follow.

Stella Kyriakides, President of Europa Donna

We want to live, not just survive

The session on Discrimination in the Workplace was like no other. Delegates who had remained quiet and attentive throughout the weekend sprang to their feet to tell their stories. Ekke Buechler of the Austrian prostate cancer group Selbsthilfe Prostatakrebs talked about the attitude of a union rep at his workplace who had special responsibility for disabilities. "I went to this man after my prostatectomy, to ask for some help securing a less physically demanding job. He told me: 'You're looking good, you have all your arms and legs, you're not blind – perhaps you could lose some weight. So what's the problem?' "

He added: "It's ironic that so many cancer patients are getting back their lives thanks to scientific research, only to find civil society then denying them their lives by excluding them."

Catherine Casserley, of the UK Disability Rights Commission, said that all but four countries in Europe have yet to introduce laws to comply with the EU Disability Rights Directive, for which there is a deadline of 2006. She urged delegates to campaign to ensure that their governments define "disability" in such a way as to include the sort of chronic, often intermittent, and almost always invisible impairments suffered by cancer patients.

Many delegates had strong feelings on whether or not cancer patients wanted to be labelled

"disabled," but agreed that ECPC should work within the European Disability Forum, and that everyone had to stick together to promote a culture, backed by legislation, that supports cancer patients who want to remain in work.

ECPC Chairman Lynn Faulds Wood

Strategic alliances

ECPC Chairman Lynn Faulds Wood spoke of the need to form strategic alliances with people working within healthcare systems, research institutions, the pharmaceutical industry, and politics. Few of these professionals, she argued, have the single-minded determination that has motivated her ever since the day she was told that she stood only a 34% chance of surviving bowel cancer, and had to face the prospect of her three-year-old son growing up without her. "That," said Lynn "is what we patients bring to the table."

Before she was diagnosed, Lynn's general practitioner told her she had nothing to worry about. Later on, using her experience as an investigative journalist, she discovered that, the world over, the advice doctors are given on how to differentiate bowel cancer from other bowel disorders has little backing in research. So she formed a strategic alliance with a number of specialists, to find out more about the key warning symptoms doctors should look for. "Just a few patients can change the world a little bit," she said, "if we work in alliance with others."

Two patient advocates, Sandy Craine and Elizabeth Rees, told the story of a similar strategic alliance they put together in the UK to fight for the right of all CML patients to be prescribed Glivec, free of charge. Their hard fought battle was won because they campaigned alongside their doctors and the drugs company Novartis.

How best to work with drugs companies was seen as a tricky question. Some delegates said their groups were wary of inappropriate pressure, and would never accept funding from the industry. Others said they couldn't survive without it and they didn't feel too compromised. Some of the activities of the ECPC are supported through no-strings grants from six drugs companies in accordance with the sort of transparent funding policy that is increasingly being adopted by patient groups (see www.ecpc-online.org/policy_funding.html). Lynn Faulds Wood said: "The interests of patients and the industry are by no means identical, and where they diverge we say so. But where they do coincide, it is important that we seize any opportunity to collaborate to achieve our ends."

"Just a few patients can change the world a little bit, if we work in alliance with others"

*The European Cancer Patient Coalition (**www.ecpc-online.org**) is the voice of European Cancer Patients.*
It was established in 2003 to represent the views of cancer patients in the European healthcare debate and to provide a forum for European cancer patients to exchange information and share best practice experiences.
Membership is open to organisations dedicated to advocacy, support and care of cancer patients and their carers.
ECPC can be contacted at:
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info@ecpc-online.org

Why I got involved in cancer advocacy: Four ECPC delegates tell their stories

Eoghan Cahill

Men Against Cancer, Ireland

Eoghan Cahill, from County Cavan in Ireland, had to call on all his reserves of stubborn determination and his creative skills as a commercial artist, in order to get home from hospital with his self-esteem intact.

His doctor had warned him that surgery for prostate cancer risked leaving him impotent and incontinent. But he had also told him the incontinence was nothing to worry about, "You will have all the advice you need." He didn't get advice. What he got was a massive nappy that hardly fitted into his trousers, and advertised to the passing world: 'This man has lost control of his bladder'. Eoghan was having none of it. "By this time," he said, "I'd spent three weeks in hospital, and had seen how men had come in for their operation, proud and tall, and had left bewildered and humiliated, some of them leaving dribbles of urine on the hospital floor before they'd even started their journeys home."

Armed only with a pair of scissors, a roll of sticky tape, some plastic bags and the offending giant nappy, he cut, stuck, fashioned and moulded himself an effective lining for his pants, invisible to the outside world. And he went home. In the end, it was his local chemist who led him to the advice that had been so disastrously lacking following surgery. He put Eoghan in touch with a community nurse who happened to specialise in problems of incontinence. She brought neat absorbent pouches and showed him how to regain bladder control through strengthening his pelvic floor muscles. One man's post prostatectomy problems had been greatly alleviated. But he was still very angry.

The story of how Eoghan moved to co-founding MAC (Men Against Cancer), eventually teaming up with the European prostate cancer advocacy group Europa Uomo and attending the ECPC conference, could match any told of a pleasant evening in a (smoke-free) Irish pub. One small part of it involved a throwaway comment by an eminent oncologist addressing a conference of support groups called by the Irish Cancer Society. The oncologist said: "We all know how backward men are about coming forward for medical treatment…". For Eoghan, who had been through a

"Just to talk to someone who's been there, done that and wears the T-shirt lifts a huge load of fear off you"

personal battle to get information and who was attending this meeting uninvited, that was the last straw. "That comment just pressed my button," he said. "I stood up and shouted 'THAT IS NOT TRUE!' and the room went silent. I said: 'If men have a tendency to try to play down problems with their waterworks, it's because they don't know the dangers until it's too late. And whose fault is this?' I asked, and I pointed around the room, 'Every single one of you professionals in this room have known for years the true story and have never once made the effort to set up an awareness campaign to make men of this country aware of the dangers of prostate and testicular cancer. And shame on you!'"

Clearly Eoghan was not the only angry man in the room, because he sat down to a rousing applause – even the eminent oncologist joined in. After the meeting, the Chief Executive of the Irish Cancer Society collared Eoghan and his friend, and Men Against Cancer (MAC) was born.

Today, Eoghan and his colleagues in MAC remain a vital source of information and support. Ireland is now running its first prostate and testicular cancer awareness campaign, using plenty of humour to encourage men to think about the upkeep of their bodies the way they do the maintenance of their cars.

What did Eoghan learn from the ECPC meeting? "I learned from the experience of others about communication, about dealing with politicians and about creating powerful alliances by combining small groups together, as we did with Europa Uomo, which will soon have groups from 13 different countries."

And how will he use it? "I would like to see the current awareness campaign expanded and continually refreshed, so it's not just a one-off effort. I would like to see better training of frontline primary care staff to improve early detection, and addressing the question of over-treatment is very important. But at the end of the day, we are patient support groups, and we mustn't forget why we are here. Because I remember vividly what a dark, dark journey I travelled. It doesn't matter how loving and caring your family is. Just to talk to someone who's been there, done that and wears the T-shirt lifts a huge load of fear off you."

Lt. Gen.

Antonio Avelino Pereira Pinto

Portuguese Association of Patients with Prostate Diseases

When General Pinto founded the Portuguese Association of Patients with Prostate Diseases one and half years ago, he did so somewhat reluctantly. As far as personal cancer journeys go, his had been relatively free of trauma. He had a good doctor, who, on diagnosis, had encouraged him to seek a second opinion (an offer General Pinto declined) and then carefully went through the options: Surgery would deal with the cancer, but carried a 60% risk of impotence and a 15% risk of incontinence. Without surgery, because the cancer was relatively slow-growing, it could be contained for a good 10 years or so by regular medication, but in the end it would probably be fatal.

General Pinto, who was 62 at the time, took the very personal decision to forego surgery, and he set about enjoying the life he had left to him – something he does very well. "I told my wife I had a prostate problem. I never said it was cancer,

"What could I do? He has saved my life for 12 years …
I couldn't say No. As a military man, I accepted the mission."

because I don't want her to worry. If she is going to wake up every morning and have to look closely at me to see whether her husband was dying, she would have died before me!"

Today, he has been living very happily with cancer for more than 12 years, and his illness impinges very little on his life.

So when, in 2002, his doctor begged him to start up a prostate cancer organisation in Portugal, he felt little of the sense of personal anger and injustice that motivates many cancer advocates. He did, however, recognise that many lives are being lost needlessly. "Every day, between five and six men die of prostate cancer, and there are around 140,000 currently diagnosed with the disease. Yet very few men in my country know what prostate cancer is. Most don't even know they have a prostate," he says.

General Pinto's doctor was insistent, arguing that it is crucial that patients speak out about their disease and provide a point of information for men who may be reluctant to visit their doctor. With his gregarious and optimistic outlook on life, Pinto, argued the doctor, was the man for the mission. "What could I do?" said Pinto, "He has saved my life for 12 years. I couldn't say 'No'. As a military man, I accepted the mission."

He set about the task in a systematic way. He set up the Portuguese Association of Patients with Prostate Diseases, and recruited patients via their urologists. The Association now has between 30 and 40 members, but is still at a very early stage. "When we have 100 members, we will set up proper statutes and functions." He runs a help and information line from his home, and has even fielded calls from France. He is in the process of setting up a website. But he still works very much alone, so when his doctor told him about meetings of the ECPC and of Europa Uomo (which held its founding meeting in Milan), he was curious and eager to attend. He learned a lot. For a start, he met a woman from a breast cancer organisation in Portugal that he had never known about, and she told him about other groups, for ovarian and colon cancer. "When I return, I will contact these organisations, and we will try to decide how we can lobby together".

"I have found out so much from this meeting about how people help patients. I will take the information back with me and study it and decide how to proceed. I want to start a newsletter with information about this seminar to send to my members."

One of General Pinto's priorities has been lobbying for prostate cancer to be classified as a chronic disease for the purpose of eligibility for free treatment. His present treatment, for example, costs him around 30 euro a month.

He is also keen to spread information among Portugal's general practitioners, so that they pick up symptoms quicker and have a better understanding of treatment options. "The important thing is for people to be diagnosed and treated earlier, and for them to realise that life does not stop because you are diagnosed with prostate cancer. Life is there to be lived."

As for his personal goals, "My aim is to live three years more, so I will complete 50 years of marriage, and my wife and I can celebrate our golden anniversary."

You sense that this is a man who will accomplish his mission.

Anna Valachova

breast cancer patient, Slovakia

Anna Valachova is a breast cancer survivor from Nitra in Slovakia. She survived because she knew someone who was able to get her seen by a specialist for a second opinion. She now wants to make sure that everyone in Slovakia knows how to get access to good cancer treatment when they need it.

"I went to my doctor with a lump in my breast. He told me not to worry. 'Many women have lumps like this' he said. I wasn't satisfied, and I told him my

"Very few people know …that you can ask your general practitioner to refer you to breast screening even if there is no screening centre in your area, and that if they refuse this request, you can go elsewhere."

sister had been diagnosed with breast cancer 10 years previously. He just told me to 'wait and see'."
Luckily, Anna had a friend who was on good terms with a cancer specialist. She went to see him at Bratislava's cancer hospital, and underwent all her tests on the same day under the same roof. Four days later a lump measuring 2.8 cm was surgically removed, and two weeks later she was started on a course of adjuvant treatment combining radio- and chemotherapy. That was in 1997. Because she is considered to be genetically at high risk, she still attends a check up every three months. Once a year she has tests to check for metastases.
Anna knows that not everyone is as lucky as she is, and every year people are dying simply because they did not have the information they needed when they needed it. "The most important thing," she says, "is to inform people about all cancers. Very few people know, for instance, that you can ask your general practitioner to refer you to breast screening even if there is no screening centre in your area, and that if they refuse this request, you can go elsewhere."

When her doctor told her about the ECPC meeting in Milan, she saw it as a great opportunity to set something up in Slovakia. "I am so glad I came," she said. "Before coming here, I discussed with my doctor the possibility of setting up an organisation and developing a cancer information website. After this meeting, I have a lot of new ideas. I want to go to schools to raise awareness about cancer among children – they have access to the Internet at school and will be able to pass on information about prevention and treatment to their families. I have spoken to Europa Donna about working with them."
And her source of recruits for Slovakia's new cancer advocacy group? – Bratislava's oncology hospital. "It's best if we are all patients or former patients," says Anna, "We understand and feel things differently."

Jan Geissler

Leukaemie-Online.de, Germany

Jan is a young information technology (IT) professional from Bietigheim. When he was diagnosed with chronic myeloid leukaemia (CML) three years ago, his doctor recommended a bone marrow transplant. Jan was not happy with the idea, and sought a second opinion. Again, he was told: if you want a cure, transplantation is the only option. However, Jan's first doctor had mentioned a drug that was still under development – Glivec (imatinib), then known only as STI-571 and not available on the market – and Jan determined to find out more.
He turned to the Internet, and found nothing in German. Luckily, his grasp of English was just about sufficient to allow him to wade through the rapidly increasing amount of information coming onto the Web from patients, academics and researchers. He located a paper written by a doctor in Mannheim and e-mailed him asking for more information. This doctor, who turned out to be one of the best CML experts in Germany, phoned him, and after a conversation

lasting two hours, Jan knew a great deal more.

The Mannheim university hospital was running an international trial comparing Interferon alone (the standard drug at that time) with STI-571 (now known as Glivec). The new drug was showing terrific early results, but no-one knew how it would behave in the longer term. So far it had largely been tested on patients who had failed to respond to Interferon, but never on patients like Jan who had undergone no previous treatment. As this trial was already closed, joining a small trial combining STI-571 with Interferon was his only option to get access to the new drug.

Jan, the scientist, took a hard look at the statistics and opted to join the trial: "I calculated all the probability values, and concluded that my chances of dying would have been much higher going directly into transplantation." And so far, that has turned out to be a very good choice. "During almost three years of treatment I have pretty much lived my normal life. I have hardly any side effects, my life has returned to normal."

Like so many patients involved in the Glivec trials, Jan wanted to make sure other patients benefited from the information he had. So being an IT professional, it was a simple matter to set up a new website: Leukaemie-Online.de.

And in a matter of weeks, Europe's 100 million or so German-speaking population had their first access to information on CML in a language they could understand.

With the help of a few other volunteers, Jan sifts through information he picks up from newsletters, health professionals and patients all over the world, and in particular from US and Asian online support groups, and selects the stuff most relevant to patients in Germany. He then translates it and posts it up on his site, where it is accessed by thousands of patients at a rate of 45,000 hits a month.

Jan is convinced that many German doctors are continuing to recommend bone marrow transplants to their CML patients as a first line of treatment. "Doctors are no different to any other profession," he says. "About 80% of them are just doing their job, some 10% are alarmingly ill-informed, and about 10% are brilliant and have a mission.

"The problem is among the 80%, because they don't just deal with CML, they deal with all kinds of cancer, and they are often slow to pick up on new developments which have revolutionised leukaemia treatment in recent years. The mission of Leukaemie-Online.de is therefore to inform patients about all their options, so they can challenge their doctors, and ask why they can't try this treatment or another. If the doctor has a good reason, fine. But if not, the patient should insist on exploring the options further."

Jan is a founding member of ECPC, and he got a lot of benefit from the meeting. He met in person fellow CML patients from Canada, UK and Israel whom he already knew through Internet exchanges, and he found out about international groups working in a similar field. "I had a picture of what was happening in Germany, but not Europe wide and not in other cancers." He is now convinced about the need for European cancer patients to join forces. "When I saw what happened with the EU clinical trials directive, which is now heavily damaging life-saving research in Europe, I can see that we have to work at the level of the EU and not only at national level. I think it is very important not only to have CML support groups or breast cancer support groups, and not only to have German or UK support groups, but to have a European perspective for all cancer patients.

That is why I became a founding member of ECPC."

"When I saw what happened with the EU clinical trials directive, which is heavily damaging life-saving research in Europe, I can see that we have to work at the level of the EU and not only at national level."

Betting on e-collaboration

Interview with Dr Alex Jadad

➜ by Anna Wagstaff

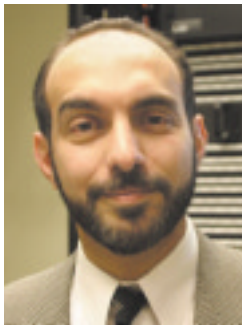
All over the world, communities are grappling in isolation with universal questions of how to prevent cancer and improve the lives of patients. But is there any reason, in this Internet age, why we should not share ideas and adapt effective strategies to local conditions. **Alex Jadad**, Director of the Centre for Global eHealth Innovation, believes there is not. And he is trying to prove it.

Global collaboration is an elusive goals pursued by many people for many different ends. What makes you so convinced it can work in the case of cancer?

ALEX JADAD I'm not convinced it will work, but it's worth a try and I'm giving it my best shot. We are all very good at believing that we are dealing with unique issues in every country, so we keep competing with one another to reinvent the wheel. Now with the Internet, we have a tool that has the potential to give communities everywhere the same access to vast quantities of vital knowledge and information and the means to communicate with one another. The problem is that the digital divide is actually widening, and most of the world still has no Internet access, nor the ability to use the information it provides. So I am trying to bring people located in strategic areas of the world together, and see whether we can make a real difference.

There are all manner of urgent health issues facing communities around the world. Why focus on cancer?

ALEX JADAD The Centre for Global eHealth Innovation, in Toronto, does not only deal with cancer, but cancer is a central interest. One reason for this is that I am a specialist in supportive case and work mainly with cancer patients. A few years ago the International Union Against Cancer [UICC] asked me to co-chair a think tank promoting global ways of working, which means I have a huge international cancer organisation interested and supporting this work. Another reason is that cancer presents unique opportunities for widespread collaboration, because it is a universal problem that crosses age groups, income levels and countries and it covers the whole spectrum of health services, from prevention to bereavement. The fact that cancer is so expensive to treat also means that governments are prepared to invest large sums in prevention.



If we can pool our ideas on ways to tackle tobacco cessation, this could have an impact, for instance, on the one and a half billion strong population of China, where tobacco use is nearing the levels we once had in Western Europe and North America.

LIBA TAYLOR / CORBIS / CONTRASTO

Centre like this one Hargeysa, Somalia, are bringing Inernet access to many parts of rural Africa

In what fields are you trying to promote collaboration?

ALEX JADAD We are concentrating initially on tobacco cessation and pain management as these are the two main issues that are widely seen as universal and transcend every boundary.

Tobacco is a huge problem everywhere, and the reasons for smoking are the same the world over. However, in some places we have had more success reducing tobacco consumption than in others. So rather than leaving each individual country, or community to work out, from scratch, ways of tackling the industry and educating young people about the dangers of smoking, we want to use the Internet to gather success stories from all over the world.

The UICC has already established a huge international network – Global Link – that connects people interested in tobacco cessation. We are now concentrating our efforts on creating what we call 'e-tool kits' to help make strategies that worked in one country equally effective in other cultural environments.

The other focus is pain management. In many countries morphine is managed as an illegal drug, and it is still very difficult to prescribe. But some countries, such as Colombia where I come from, have managed to solve the problem of how to prescribe morphine. So there is an opportunity to work with advocacy groups, to make them aware of the sort of regulations that have been successfully introduced in other parts of the world.

There are also many myths and cultural barriers that deter patients from taking effective pain relief,

If we collaborate, then language is not an insuperable problem

and these are surprisingly similar the world over. Some people fear pain relief might make them die sooner or turn them into zombies. Others see pain as an inevitable part of cancer, or may not wish to be seen as wimps or distract their doctors from treating the disease. So here is an important issue that affects the quality of life of 75% of cancer patients and which we can improve simply by getting the message across that pain can be stopped effectively. Research has shown that it takes around 10–15 years for an innovation that has been proved successful in one environment to be taken up and used effectively elsewhere. We can't afford this time lag in cancer, so we hope that by making these e-tool kits available we will be able to speed up the learning and adaptation process.

What is being done to bring Internet technology to low-tech communities with poor infrastructures?

ALEX JADAD A lot. The United Nations has turned parts of India into a living lab for experiments on how to widen access to the Internet, and there are now more than 2000 different projects to mobilise the community behind these efforts. One of these is an attempt to extend Internet access from towns to the surrounding rural areas by fitting antennae on local buses. The antennae provide a wireless (Wi-Fi) connection for anyone within a 300-metre radius, which means that villagers will be able to sign on for short periods, two or three times a day, as the buses drive around their village. In some rural areas in Africa there are now "telecommunity centres" with phones, Internet access, photocopiers, all under one roof. These initiatives have many different purposes: to support farming communities, encourage small businesses, promote basic health and hygiene, bring information to schools… My question is: why not use the same resources to promote cancer prevention and disseminate information on palliative care?

This is what I mean about global collaborative effort – looking at what is there and working together to achieve goals that go beyond what was originally intended. It's important to remember that we are not talking about a computer in every home. Community workers, health workers and teachers can all act as "information brokers," downloading what they need, adapting it and getting the message across in appropriate ways.

> So instead of everyone starting from scratch and making the same mistakes, each community can benefit from the expertise and success of others

Even if these communities do get Internet access, what good will it do them? The information is almost entirely in a language they can't understand, and written in the contexts of economic, cultural and health environments that differ radically from their own.

ALEX JADAD If we collaborate, then language is not an insuperable problem. Toronto, where I work, is a good example. It is like a mini-world with 150 ethno-cultural communities. Here we have a telephone service called 211, which provides a translation service in 100 different languages, 24 hours a day, seven days a week. It is expensive, and paid for partly by the state and the phone company, and partly by charitable trusts. But it serves 3000 community groups and support agencies in the city, so there are huge economies of scale. None of the groups could provide this service alone, but through collaboration, they are able to overcome language barriers even in the most linguistically diverse city in the world.

But the problem goes well beyond language. If we are to provide information on cancer care and prevention to Africa's Swahili-speaking communities, that information will have to be relevant to the local culture and conditions. Here too, collaboration is everything. All it takes is for one local community health team to work with us to adapt existing materials for their own use. The materials can then be made available via the Internet to all Swahili speaking communities of Africa, and health care workers or teachers in these communities can then download them and use them and then introduce their own modifications on the basis of their own experience, and pass these on to others. So instead of everyone starting from scratch and making the same mistakes, each community can benefit from the expertise and success of others.

Much of what we do at the Centre therefore focuses on helping people take information developed elsewhere and adapt it for local use. This is the purpose of the "e-tool kits." They consist of the raw information, strategies for adapting the information (how to sift out what is irrelevant and make it locally pertinent), and options for getting the message across. If the material is to be posted on a website, it will need to be designed and organised in a certain way, if it is for downloading and photocopying for use in schools or clinics, then it will need presenting in a different way. Or one may want to use local television or radio to spread the message, in which case we have the facilities to achieve this in Toronto, including 400 actors and 1000 patients and their families from very diverse backgrounds who speak 52 different languages between them.

Does your work have any relevance for Europe?

ALEX JADAD The potential for using the Internet and other information technologies in health work is now a major debate in both Europe and North America. The European School of Oncology (ESO) took the important step last year of bringing together some of the key voices at the First Conference on Cancer on the Internet, held in New York last September, and I have now been invited to co-chair the Second Conference, which, among other issues, will address fostering global collaboration and promoting digital inclusion.

In Europe, the Internet may not be the main answer to improving access to information, at least not yet. In many European countries, fewer than one in three families have access to the Internet – compared to almost nine out of ten in North America. The mobile phone, however, is becoming almost universal, certainly for the younger generation, but increasingly for seniors as well. And it is an incredibly powerful way to communicate – mobile phones today can send and receive e-mails and text messages, and can be used to watch television programmes and videoclips.

We wish to help local organisations develop ways of exploiting mobile phones – perhaps in conjunction with the Internet – to disseminate information about cancer treatment and prevention. The key is finding out how people wish to receive the information. Do they want audiovisual clips? Would they prefer text – large type or small? Everything we do is subjected to "usability" tests to ensure the service will be easy to use.

At what point will you know whether e-collaboration can produce the health benefits you hope for?

ALEX JADAD We've achieved a great deal in a short period of time. Through the UICC we have access to hundreds of organisations working in the area of cancer, tobacco cessation and pain, and we have set up the infrastructure to link them together. We have ESO in Europe, we are collaborating with six regional Health Ministries in Spain, one of which wants to work with us to develop a telehealth initiative for North Africa and Latin America. India is likely to take the lead on pain management tool kits.

We need to think big, act small and deliver quickly. Let's try it – what did we learn? Make some changes – what did we learn? And hopefully after four or five cycles of doing and learning, we will have the basis for something effective that can be used by groups all over the world to make a real difference.

More information on the Centre for Global eHealth Innovation can be found at: www.ehealthinnovation.org