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Jan Foubert

➜ Jan Foubert: champion of cancer nursing ➜ Would the right to a second opinion make any difference to patient care? ➜ How will EMEA use its new powers of conditional approval? ➜ Tackling the growing survival gap between eastern and western Europe

Contents

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A question of public trust

Kathy Redmond ■ EDITOR

Recent headlines in the UK press have again put the issue of pharmaceutical company sponsorship of cancer initiatives under the spotlight, rekindling the debate about its dangers and its merits. Whenever a non-profit advocacy, patient or professional group opens itself up to accusations that it is acting as a front for a commercial company, all groups and all companies find themselves under suspicion. But there are many reasons to resist a knee-jerk reaction on either side to pull back from any form of cooperation.

Pharmaceutical companies are in the cancer business to make money. And yet as long as we need better drugs to address existing unmet need in cancer, their interests overlap with many non-profit groups. Commercial firms have a long tradition of supporting advocacy groups and campaigns, some of which have had a sustained impact on the quality of care that cancer patients receive. These campaigns can benefit from the industry's resources and experience in research, marketing and communications as well as financial support. But they can also open themselves up to accusations of bias and hidden agendas, which can backfire badly on the campaign.

Some voices in this debate argue that it is impossible to prove there is no hidden agenda, and that any form of partnership with commercial interests fatally compromises the independence of non-profit groups. But independence is of little use without the resources to run a democratic organisation that can make an impact where it matters.

In an ideal world, all the stakeholders active in the cancer arena should be able to work constructively towards shared goals, while acknowledging areas of conflicting interests. The challenge is to define how the corporate world can work with the non-profit world without undermining the reputation of all involved.

It may be impossible ever to allay the suspicions of hardline sceptics, but public confidence in general may be satisfied with answers to the following questions: which commercial concerns are contributing what, and what are they getting in return? Who decides on the agenda and the way it is pursued, and to whom are they accountable?

Many non-profit cancer groups are now negotiating a more arm's length relationship with their industry sponsors, developing policies that clearly spell out the rules of engagement. Many companies and industry associations are going through similar exercises. Some voices have long been calling for a single, simple set of agreed standards to protect those who follow best practice from being tainted by those who do not. There are many obstacles to achieving such a goal, but given what is at stake, it is important that all stakeholders take a fresh look at the way forward. Otherwise, a build up of negative headlines could prompt politicians to take unilateral action.

Jan Foubert: champion of cancer nursing

Marc Beishon

Jan Foubert knows the value of a good cancer nurse – someone who understands the patient's needs, knows how to help them cope with the disease, symptoms and side-effects and has skills to apply that knowledge. He believes it's up to Europe's nurses to redefine their role in cancer care – but he'd also welcome a bit more support from the other oncology disciplines.

If there is one factor that can help a core oncology specialty to develop around Europe it is consistent and long-term leadership, which European cancer nurses have enjoyed in recent years in the form of Jan Foubert. His credentials include a background in paediatric oncology nursing, academic nursing positions at the Erasmus institute of higher education and the Free University in Brussels, and he is the immediate past president and longstanding board member of EONS, the European Oncology Nursing Society. Most recently, the US Oncology Nursing Society selected him for their International Award for Contributions to Cancer Care, which he will receive at the ONS Annual Congress next April.

It is, however, a new role at EONS that will cement his relationship with the nursing cause in Europe. "I have accepted an executive director's post, that will allow the society to build on all the projects and development work I've been involved with as a board member," he says. While the details of the new post are to be decided – he will also continue with his teaching duties in part – his direction is unequivocal. "I've just turned down two other jobs so I can work with EONS – a director's post at FECS (the Federation of European Cancer Societies) and a principal's position at the university."

Those who have encountered Foubert on the conference circuit and as a board member of EONS and FECS will not be surprised by his decision. While always open to discussion, he has long been of the view that Europe's oncology nurses – and there are around 30,000 in EONS – need a strong, independent voice, and they have enjoyed precious little support from the medical oncology community, despite the supposed rise of multidisciplinary working. Further, although oncology nursing has developed as a specialty in a few countries, the overall picture is very fragmented in terms of recognition, educational opportunities and requirements, and clinical knowledge and research.

In fact, Foubert feels there is an urgent need to address what he calls a 'loss of identity' among the nursing community generally. "A shocking definition I've heard of a nurse is that they do things that can also be done by others," he says. "What a lot of nurses still do goes back to the days of Florence

ELIGIO PAONI / CONTRASTO

"Nurses complain about respect and image – but we have to create our own image and earn respect"

Too often, trainee nurses bursting with ideas end up in units where there is little scope to change things

Nightingale – basic care and being dependent on doctors to tell them what to do." While there are, of course, many specialised and advanced posts in oncology – such as pain management and tumour-specific roles, and some senior nurses acting as 'mini-doctors', as Foubert puts it – there is a danger of the bulk of bedside nursing remaining stuck in an assistant nursing role, suffering from a lack of knowledge and empowerment. "Governments will say, 'Why should we pay so many registered nurses when one or two can coordinate the care?'"

The present-day situation is exacerbated, he adds, by societal changes that have seen nurses less valued than they were. "The uniform and presence once meant you were respected – now society sees nursing as any other job. Nurses often complain about respect and image – but we have to create our own image and earn respect."

It is the majority – the bedside oncology nurse – who Foubert has most in mind in his work to help raise the profile and professional attainment of nursing. Apart from his involvement in the politics and strategic agenda setting for EONS, his teaching experience has no doubt informed the development of the society's most important programmes so far. These include educational initiatives such as TITAN, which deals with thrombocytopoenia, anaemia and neutropoenia – conditions where nurses can play key treatment roles – taught in a way that shows how such potentially forbidding topics can be shaped to be of practical value and not discarded as being too theoretical.

Foubert's own pathway into a nursing career was quite remarkable. Brought up in Germany, he had initial ideas about being a psychologist, until a friend of his mother, a night sister at a hospital, invited him to spend a shift with her – where someone died. "He was put in bed in a bathroom, with no one with him. I thought, 'This can't be right.'" Then in a school holiday he found himself visiting a nursing home for older people with dementia, again through a family contact. "The director was looking for holiday help – I went on a tour with my mother and in one room there were four women, one of whom was spreading faeces on a hot radiator. I stayed and did the evening shift. My mother couldn't understand it."

This highly unlikely holiday job for a teenage boy – which was probably illegal – was nevertheless highly stimulating, although Foubert says he had to grow up rather rapidly. He was determined then to qualify as a nurse, which he duly did at a nursing school in Brussels, and then went to a new hospital, Queen Fabiola Children's University Hospital, also in Belgium, as a paediatric intensive care nurse. University training, as he often says to his students today, hardly prepares you for the realities of such a job, but in this unit he was able to learn quickly about all manner of high-, medium- and low-intensive care situations.

Foubert was also able to fit in a master's degree, specialising in hospital science, which also had an educational option, meaning he was then equipped to teach other nurses. "The hospital director asked me to build up hygiene practices in the hospital, and then one day called me in and offered me the head nurse position in the paediatric oncology ward – I had to take it there and then." He notes: "As a new nurse you have to be visible to the decision makers so that they can see that you have competencies that can be of use for the organisation. Don't follow the crowd."

Foubert realised he knew next to nothing about oncology. "The doctors might as well have been talking Chinese," he says, adding that today's nurses receive little oncology teaching on undergraduate courses, which hardly stimulates them to look at specialised postgraduate cancer options. In a month or so he had read up on cancer to the extent that he felt he knew more than most on the unit, and brought his intensive care skills to bear – showing other nurses how to perform a resuscitation in one case and how to monitor and assess children in a critical situation on an oncology ward.

He also led the reorganisation of the unit. Nurses

were working on only one of several areas, such as ambulant care or closed bone marrow treatment rooms, and they were asked to vary their work. This proved unpopular with some (who then left). Some evidence-based practice was brought in – such as the use of specially prepared sterile food for bone marrow patients. "It was from my master's study that I showed the food we could get from commercial sources was much safer than food we prepared ourselves – all we needed was a decent kitchen with a store of safe food in a fridge, and a microwave."

These two themes – challenging ingrained habits and introducing evidence-based nursing – have become central to Foubert's views about developing nursing practice. "If there is one profession that is difficult to change, it is nursing," he says. "Nurse training is about a lot of theories and models – but when you go into practice you don't often see them." Too often, he reckons, trainee nurses bursting with ideas end up in units where there is little scope to change things, although there are some places where being assertive and dynamic is welcome. "But the most frustrating thing a new nurse hears is, 'We have always done it this way.'"

Meanwhile, at the children's hospital, Foubert and a doctor colleague who had been working in the US brought in outside finance to equip the oncology department with TVs and toys, and decent bedside clinical equipment. "I realised that to build a unit you need charitable donations, which we obtained from business people. It became an exemplar unit, visited once by Princess Diana. Everyone wanted to see it."

It was on a Europe Against Cancer course that Foubert was noticed by the director of the Jules Bordet Institute in Brussels, Belgium's only dedicated cancer centre, and he moved there as a nurse manager, taking a step away from the bedside. "At the time this was an ideal place – one of the few hospitals doing rehabilitation, pain management, stoma therapy, breast cancer nursing and so on. It was a pioneer, particularly in rehabilitation under psycho-oncologist Darius Razavi."

However, Foubert says that it is all too easy to lose leadership status, which he feels happened at Jules Bordet from his nursing perspective. "You need to keep on top of protocols, standard care plans, clinical pathways and quality – things you can measure – and not just take care of the basic needs of patients, which makes oncology nursing no different from general nursing. I was busy with nursing shortages, and generally the hospital, like many others, was firefighting and found it hard to go forward with nursing development."

With other cancer centres springing up in Belgium, all starting to do similar things, adds Foubert, it becomes difficult to maintain a unique reference presence. His main focus there was as a nurse champion, visiting every unit each day, and paying particular attention to the needs of head nurses, who he says can often be in very isolated positions.

Foubert went on to become a continuing education coordinator at Jules Bordet, while starting a teaching career as a lecturer in nursing and midwifery at Erasmus. He still has a strong link with Jules Bordet, however, as he runs a fatigue clinic there half a day each week – fatigue is a special

FATIGUE – GOOD ADVICE IS KEY

Fatigue has become one of the more difficult side-effects for healthcare professionals to tackle, despite it being one of the most common complaints of cancer patients. "Doctors and nurses tend not to be interested in it because its origin is not known – they prefer to treat symptoms such as pain, where they know they can do something," says Foubert. At the recent World Congress of Psycho-Oncology, he presented a case study of someone with fatigue and borderline anaemia. "The only questions from doctors were about the anaemia – it was a psychologist who asked me how you measure stress levels and was interested in the problem of fatigue in cancer survivors.

"Also, what I've learnt in my fatigue clinic is that most studies on fatigue have been done on patients undergoing treatment, but it can continue in people who are cured or no longer treated – there is little available on this population in the literature."

Fatigue management should be integrated as a standard care plan, as with pain management – but it is not happening in most places, according to Foubert. He says nurses are well placed to develop management strategies by approaching the problem as a lifestyle issue, in a similar way to a dietician advising on weight loss. "If you want to lose weight I can coach and motivate you – but you are the only one who can lose weight. Fatigue is the same – you have to change your lifestyle and habits and think about how you deal with reduced energy."
This can touch on painful personal issues. "When I ask women with families, 'When was the last time you did something for yourself?,' they often start crying. When someone is diagnosed with cancer, the emphasis is on the war against it – the treatment – and not how you come to terms with it. We have to change our minds about lifestyle issues being too difficult to tackle."

"A bedside nurse wants practical, interactive training that they can actually implement"

interest and one especially relevant to oncology nursing (see box).

At the same time, an involvement with EONS started to take off. Initially, he had little knowledge of European oncology societies, or conferences such as ECCO (the European Cancer Conference). That was all to change as he quickly made his presence felt, soon being invited to become an EONS board member.

"When I first became involved, EONS was looking at the status of oncology nurses, especially in eastern European countries. It's still the case that there are major differences in status in Europe between east and west and north and south – and what I saw was that EONS could only be important if we could reach the bedside nurse, those who do not normally have the opportunity to go to conferences. That was my goal from day one, and I'm happy to report that, by the time my presidency of EONS came to an end, we had increased membership to 32 national oncology bodies from 28 countries."

EONS has a core strategy under the acronym CARE – meaning Communications, influencing the Agenda, Research and Education – and education has been the most important main activity, and should remain so, according to Foubert. "It is the biggest need of European oncology nurses," he says, noting a number of challenges, from increasingly specialised cancer treatments, to shorter hospital stays (which may mean community nurses needing some cancer expertise), to changing role boundaries in hospitals, with some countries allowing what were previously medical procedures to be carried out by nurses – those 'mini-doctors'. He would also like EONS to be the platform to launch specialist nursing groups, such as for breast cancer, palliative care and geriatric oncology.

According to Foubert, what has been lacking are educational packages that address real needs – rather than supposed requirements – and also materials that are usable across the many different cultural healthcare environments in Europe. "What used to happen was that the industry would bring out a pack, say on nausea and vomiting, for nurses, but there was no research on whether there was a need for it, and what the current state of knowledge was. Also, much educational material has come from the UK. While some of this is very valuable – such as materials on biological therapies – it is much too complicated for the bedside nurse, and of course it is written or presented in English, not a common language for many nurses. Bedside nurses don't want an all-day lecture – they want practical, interactive training that they can actually implement."

What has also been missing, he adds, is evaluation of the impact of education and the dissemination or use of the new knowledge. "We assume that people who have been educated will perform better. When I was an education manager, if a problem came up, managers said nurses need to be trained and the problem will be solved. That's nonsense."

Educational programmes at EONS, says Foubert, now emphasise needs assessment, piloting, evaluation and dissemination, and don't just assume that the training alone is enough. The first initiative was NOEP (Nutrition in Oncology Educational Program), launched in 2003, and a raft of other programmes with impressive sounding acronyms have since got underway, such as TITAN, BONE (Bisphosphonates Oncology Nurses Education), Speak Up! (dialogue with patients on nausea and vomiting) and Target (training in targeted therapies).

TITAN is being rolled out across Europe by national oncology nursing bodies. So far, more than 2,000 nurses have taken the course in 21 European countries, and it is now spreading worldwide, with Australia running its debut course last November.

Foubert – who travels to teach it himself – says cultural adaptability is a key marker of success. "I was in Slovenia at the Institute of

Team TITAN. At ECCO 13 with colleagues from the training course on thrombocytopoenia, anaemia and neutropoenia which was developed by EONS and is now taught all over the world

"The context of care in a complex situation is never the same – that's where evidence-based nursing fails"

Oncology in Ljubljana recently – they have translated the materials, and even attended the training in English on a Saturday." But there can be obstacles to overcome. "In this case, a medic called the nurse director and said they could not give this course as there is no medical doctor speaking – how can nurses possibly explain anaemia management? It was cleared, though, by asking the medical director, who supported the nurse director. This sort of situation still arises in some countries."

The educational approach that EONS is developing is also designed to fit in with the Bologna Agreement, the European Union programme that aims to standardise higher education across Europe – examples are a core curriculum for cancer in older people and the EONS post-basic core curriculum in oncology nursing.

Foubert is concerned by a global lack of attention to 'evidence-based nursing' – he feels there is a pressing need to evaluate how research can translate into effective practice in often complex care situations. Existing models, he says, "are not appropriate for the complex interventions in which the experience of the patient plays an important role in effectiveness. The context of care in a complex nursing situation is almost never the same, and that is where evidence-based nursing fails, as its principle is that the situation is always identical." The solution, he adds, lies in nurses receiving training in scientific research – and researchers in clinical research.

ELIGIO PAONI / CONTRASTO

An example close to his heart – especially with his experience with children – is the assumed need in many units to wear protective clothing when with patients, say with neutropoenia, who are at high risk of infection. As even newborns in incubators – one of the best protected places in a hospital – are colonised by many bacteria within 72 hours, evidence now points to abandoning protective isolation, with subsequent benefits for patient contact (such as being able to hold a child). But for such initiatives to become the norm, says Foubert, training, measuring and monitoring, reflection on current practices and above all nursing leadership are required.

He cites thoughts from various academics about how advanced practice nurses can 'unite the worlds of scholarship and practice,' and that nursing, like all healthcare, needs 'knowledge workers' with skills such as leadership and delegation, clinical judgement, teamwork and use of new technologies.

It all adds up to a substantial agenda – and for allies in the effort, Foubert says partnerships with patient advocacy organisations offer one of the best ways forward. "Nurses are often closer to patients than doctors, and can be of great help when patients have to make decisions," he says, adding that EONS is forming close links with leading advocacy organisations, such as Europa Donna and ECPC (European Cancer Patient Coalition). "Patients and nurses together are much stronger than on their own and have much more power than the medics at the political level," he says.

He is direct about problems he sees with doctor–patient communication. "Although most doctors say patients are important, they are often afraid to involve them in decision making. When I was on the board of FECS and other advisory boards I kept saying, 'Shouldn't we ask patients?' How else are we to know what they think and need?" A particular bugbear for him is educational material given out by nurses that has had no input from patient groups.

"Patients and nurses together have much more power than the medics at the political level"

This is not to say that nurses can assume they are close to patients – factors such as the shorter time patients spend having treatment make communications more difficult, while communications itself is a skill that needs training. Further, doctors have an advantage in that communication about, for example, a certain treatment is easier, as there is a specific goal in mind. "Years ago I did research for a patient league in Belgium that found patients were more satisfied with explanations they got from doctors, who may have carried out hundreds of the same procedure. I think that nurses often talk to patients without a clear objective in mind."

As part of solving the nurse 'identity crisis', Foubert feels that making more of being an advocate who makes time to know patients better will help, and he is an advocate himself of having nurse case managers to provide continuity and a single point of contact for a patient – currently an 'unusual role'.

On the wider stage, Foubert is organising the patient programme at the next ECCO meeting in Barcelona, previously managed by doctors. He sees this as an interim step to handing over the job to a patient organisation such as ECPC. As he says, he knows how to 'work the system', through working with FECS and EONS, and is hopeful that the patient advocacy organisations will avoid the mistake he feels that oncology doctors have made – speaking with too many voices. "It has been very difficult for politicians to know who to listen to. I hope the patient organisations will avoid having too many lobby groups."

These concerns played a role in his recent decision to turn down the offer of a director's job at FECS. "I was honoured, and may well have accepted a post to run the conference side earlier in 2006 – but I don't want to be part of lobbying, as the mission of FECS is still not clear to me."

It was certainly a brave step to offer Foubert that FECS post given his trenchant views on multidisciplinary working and the tough time he had as a board member, where he often spoke his mind. "When doctors talk about multidisciplinary teams they usually mean medics and not nurses. But nurses have to earn their place on the team – and that has to do with image, respect and leadership."

Foubert is a member of the ethics committee at the Free University of Brussels, a post he enjoys greatly and where he feels among equals. As for his lecturing post, he admits he's known as a pretty strict teacher, not tolerating lateness or backchat, but says he applies himself more as a mentor and coach, taking a lot of time to help students achieve goals. "Teaching is just explaining things – but coaching is, say, going on practice with students and working together towards objectives." Any new job for Foubert will have to accommodate at least part-time teaching – it's a love he won't relinquish.

Foubert and his partner live in Antwerp, where he's forced himself to get out to cultural activities such as opera and ballet by buying season tickets. Long cycle rides are also on the agenda, and he likes entertaining – but not with prepackaged foods. A favourite book is *The Queen and I*, by Sue Townsend, which imagines Britain's Royal Family forced to live as ordinary, poor citizens – but any thought of bringing down medics a peg or two is purely coincidental.

"I have made a clear choice about my future by taking on the daily business of EONS," says Foubert. "If I'm honest, I can't say I've been the average nurse; I'm a man and I did not encounter any major opposition at work as a nurse. Now I'm travelling everywhere, staying at the best hotels. I recognise that it's easy for me to say to nurses, 'Stand up for your rights,' but I hope I'm respected enough for nurses to know I really do mean to close the gap between the worst off and the best."

A second opinion, because there's no second chance

Marc Beishon

Patients want the option of consulting a second doctor, and the evidence shows that, for a minority of them, treatment decisions have altered significantly as a result. But could granting every patient the legal right to a second opinion tie up precious resources as each one 'shops around' in search of the opinion they want to hear?

"I wish we had checked there was nothing else we could have done" – it's one of the common regrets of the relatives of people who have died from cancer, and a reminder that worries about treatment can extend beyond the patient to possibly many years of soul searching by those left behind. Access to second opinions about diagnosis and treatment can provide vital reassurance for patients and their families at a time when they feel most vulnerable, and reassurance is a common reason for asking for referrals to other specialists, or for people seeking information independently, particularly on the Internet.

"I see three types of patients looking for second opinions on treatment," says Fatima Cardoso, a medical oncologist at the Jules Bordet Institute in Brussels. "There are those who are happy with their doctor and just want to be reassured they are having the best care. Some say they don't want their oncologist to know, just confirmation that he or she is correct. Then there is a group who are unhappy with the relationship with their doctor, and the third group are people looking for new treatments and trials, normally referred on by their oncologist. We see all these types of patient and do a lot of second opinions – I wouldn't say one reason is more common than another."

The reasons why patients seek second opinions in cancer, and in medicine generally, raise many issues, some of which have not been well researched. Clearly, the opportunities for patients to research medicine in the Internet age is of primary interest. It is increasingly changing the face of the traditional doctor–patient relationship, with healthcare becoming more 'consumer led', although many patients remain reluctant to 'distrust' their specialist, while there are still a minority of 'paternalistic' doctors who do not encourage second opinions.

Then there is the question of whether a healthcare system or society should grant legal or just moral rights to obtaining second opinions. In turn, there are questions about cost and structure – should a second opinion system be formalised for some or all complex conditions, and would there be a net cost, or would there be savings thanks to better treatment? And could there be enough capacity to carry out more formal second opinions?

A good place to start to answer these questions is to look at what data there are on where second opinions have made a difference to cancer treatment. Much of the emphasis in studies appears to be on the diagnosis of cancer – and any patient researching the issue will immediately find alarming warnings about mistakes that are made.

Second opinions in breast cancer pathology led to altered surgical therapy in 7.8% of 346 cases

Not surprisingly, these warnings appear mostly on US patient advocacy websites, and also on the websites of cancer centres in the US that offer second opinion services.

An enormous impact

For example, one of the most widely cited studies examined the impact of a mandatory second opinion for surgical pathology when cases were referred to a major cancer centre, John Hopkins Hospital, in the US, during a period in the mid-1990s. The study found that such a programme could "result in major therapeutic and prognostic modifications," and although the number of affected cases was not large, the authors considered that the rate of discrepant diagnoses "may have enormous human and financial impact," (*Cancer* 86:2426–35).

Another study, on pathology second opinions for breast cancer, 'confirmed' the benefit of a pathology second opinion, noting major changes that altered surgical therapy in 7.8% of 346 cases. Complete correlation between the initial report and the second opinion was found in just 20% of cases. However, failure to confirm a malignant diagnosis occurred in only one case, but the authors note that benign diagnoses are seldom subject to a second opinion (*Ann Surg Oncol* 9:982–987).

This is a huge topic in its own right, but it seems to be the case that patients are not as likely to seek second opinions on pathology and scan results as they are about prognosis and treatment. "Questions about the diagnosis are seldom raised by patients," says Jürgen Schultze, a radiation oncologist at Kiel University in Germany. "As I am also trained as a radiologist, I do deal with false-negative and false-positive results, but the questions are normally raised by other doctors who are not convinced that the findings of the original radiologist are right."

It is very rare to see a misdiagnosis of malignant or benign tumours adds Cardoso. "There is some controversy in the classification of some types of cancer – for example, you have a lot of discordance in grading in breast cancer and some pathologists do grade differently – and when you use techniques such as immunohistochemistry, you can get different results. I think, though, that pathologists are more advanced than clinicians in asking for second opinions among themselves – they have been in the habit for many years of exchanging slides when they are not sure about a diagnosis and will send them to experts around the world. It's much less frequent that a clinician will send a patient for a second opinion because he is not certain."

Clearly, though, there is a big difference between routine checking of pathology specimens and images for quality control purposes, and referral to a centre where different imaging and pathology tests may be done as part of a new patient consultation. Another study on 148 women who went to the University of Michigan Breast Care Center for a second consultation following a mammogram found that 7% had more cancer in the same breast, or an undiagnosed tumour in the other breast. But this was after a one-day radiology, surgery and pathology consultation, with many patients receiving additional imaging, resulting in additional or different biopsies, additional follow-up imaging and changes to treatment in 30% of the women.

The superiority of the top multidisciplinary cancer centres as places for diagnosis and treatment is hardly a

MEETING PATIENTS' NEEDS

A rare paper on the 'motives, needs and expectations' of cancer patients in the Netherlands seeking a second surgical opinion (*J Clin Oncol* 21:1492–97) found that motives differ greatly. The authors identified five relevant variables: anxiety disposition, dissatisfaction with the first specialist, preference for decision participation, need for more information, and hope and expectation that the second opinion would be different from the first.

A majority of patients (62%) were identified as having 'internal' motives, relating more to reassurance and certainty, while the remainder had 'external' motives, relating to negative experiences or unfulfilled needs.

Given that some full second opinion consultations are unnecessary and put extra strain on health services, they suggest strategies that could avoid them. These could include phone or e-mail consultation with an expert for the 'internal group', and improving communications skills – developing professionals as 'educators and collaborators' – to deal with the increasing information and participation needs of the 'external' patients.

surprise, although as referral centres they also tend to see the more complex cases, which could make discrepant results more likely. Major centres are also more likely to have access to newer techniques, such as gene-expression profiling, which can provide additional information relevant to cancer prognosis and treatment.

A milestone reported recently is the identification of a gene-expression signature for Burkitt lymphoma, which can distinguish it from Burkitt-like lymphoma (reported in the *New England Journal of Medicine*, 8 June 2006). As Paolo Vigneri, a medical oncologist at the University of Catania in Italy, comments: "They sound alike and look alike but are completely different. Diagnosis really requires an experienced pathologist, but even some experts in this NEJM study misdiagnosed it. The therapy for the two is very different, but as an oncologist, if someone tells you it's Burkitt-like or not – that's it. They are fairly rare, but the problem is that rare diseases are always less rare than you'd like and once you've encountered one you never forget it."

Rare cancers are of course more likely to be referred for second opinions, but it is the now routine treatments that may be being ignored that are probably more disturbing for patients. Cardoso does see women who have had a mastectomy when they could have had neo-adjuvant chemotherapy and a tumourectomy at a multidisciplinary centre. She feels some isolated surgeons may not be referring patients for a second consultation because they may not believe in neo-adjuvant therapy or could be afraid of losing their impact. Similarly, Schultze in Kiel sees patients who have been told by their urologist that the only treatment on offer is radical prostatectomy for advanced disease, with 20% of men then having a local recurrence – whereas he says his centre can offer a combination of external beam radiotherapy and brachytherapy, with 97% local tumour control.

In Germany, concern about existing guidelines for testicular cancer not being adequately followed has led to a new second opinion project that could also be rolled out for other tumours (see box, p17). Other countries with fledgling second opinion systems include Denmark, which has an expert panel for patients and doctors; the health insurance is obliged to pay for the treatment they recommend (see Masterpiece, *CancerWorld* September–October 2006), and Sweden, also with a recent oncology experts' initiative called 2ndview (see www.2ndview.se). There also several e-mail based question resources, especially in the US, such as 'Ask the cancer expert' at www.oncolink.com.

Who gets what

No country appears to have a national system for managing second opinions for all conditions. Some healthcare insurers in the US have had mandatory requirements for second opinions on some procedures such as mastectomy and prostatectomy to try and reduce the cost of elective surgery and to prevent unnecessary procedures. Most countries with health insurance systems have formal or informal voluntary second opinion options that are paid for in whole or in part. Insurers in the US now promote it as a patient right.

So European countries with health insurance systems, such as Germany, will pay for all or some of the cost of second or even third and more opinions, although there does not appear to be a legal right anywhere. Indeed, the UK's National Health Service explicitly states there is no legal right to a second opinion, but "a healthcare professional will rarely refuse to refer you for one unless there is sufficient reason."

In practice, access to second opinions appears to vary widely across Europe. The Euro Health Consumer Index, produced by Health Consumer Powerhouse, has graded Europe's health systems using a three-tier system, and includes 'right to second opinion for non-trivial conditions' as one of the criteria. At present, it adds Belgium, Estonia, Ireland and Latvia to the UK as countries offering no right; other countries such as Greece, Italy, Spain and Sweden only score 'yes, but difficult to

WHAT OUR READERS SAY

CancerWorld asked readers what they think about second opinions. The respondents include medical oncologists, radiation oncologists, surgeons, radiologists, cancer nurses, pathologists, patient advocates, palliative care specialists and hospital administrators among others.

- 81% answered 'yes' to the question: should all cancer patients be given access to second opinions? A quarter of those who said 'no' also ruled out any special circumstances for a second opinion.
- 66% have asked patients if they would like a second opinion.
- 35% said cancer patients can easily obtain a second opinion in their country; 18% said bureaucratic procedures hinder the process; 16% said their system does not pay for a second opinion.

A comparison between Eastern and Western Europe showed similar levels of support for the right to a second opinion (80.8% vs 87.5%), but a big difference in easy access, with 54% in the West saying patients always have access in their country and 5% saying there is no such access. The equivalent figures for Eastern Europe are 30% and 33%. The remainder indicated access is limited by region, bureaucracy or cost.

"Pathologists are more advanced than clinicians in asking for second opinions among themselves"

access due to bad information, bureaucracy or doctor negativism'. France, Germany and the Netherlands are among the countries with the highest rank for second opinions (and these countries also take the top three slots for consumer-friendly healthcare systems across all criteria). France and Germany also allow direct patient access to specialists (see www.healthpowerhouse.com).

But even in the best countries, access to a second opinion is more or less ad hoc – referral choices are entirely up to the first specialist, or can be sought by the patient via their own research or in discussion with their primary care doctor. In a survey of around 150 cancer patients from across Europe conducted at a European Cancer Patient Coalition masterclass in 2005, 50% of respondents said that bureaucracy was the main hindrance to getting a second opinion in their country. Only 13% said a second opinion was easy to obtain, 16% said it was available only from certain healthcare providers or in certain regions. Ten percent of patients said second opinions are never reimbursed in their country.

It is no wonder that patient advocacy organisations are playing a vital role as information brokers in the process. As Jesme Baird, medical director at the UK's Roy Castle Lung Cancer Foundation, comments, "Patients use us like a second opinion – they call and say, 'Here's my stage of disease, and this is what my doctor says; does this sound right?' All we can say is that it may be broadly right or wrong." However, the copious information now available on advocacy and cancer agency sites gives patients plenty of pointers on how to take steps to find an alternative consultation.

Baird adds that in a system like the UK, where access to healthcare is mainly through a primary care 'gatekeeper' (the general practitioner or GP), referrals to other specialists can take precious time and there is always the danger of vital notes and materials getting lost. "GPs may also only come across a few cases and know relatively few specialists," she says. But as an ex-oncologist herself, she adds that the two biggest advances she's seen in lung cancer in recent years are the growth of multidisciplinary teams and the role of the lung cancer nurse specialist – the latter can act as a friendly second opinion source, she says. (And in the UK, personal breast cancer information is available by e-mail from nurses at www.breastcancercare.org.uk). However, even in a big centre Baird says all options may not be explored or explained – in the UK, in particular, patients may not be told about a drug that is not funded and not in the hospital formulary.

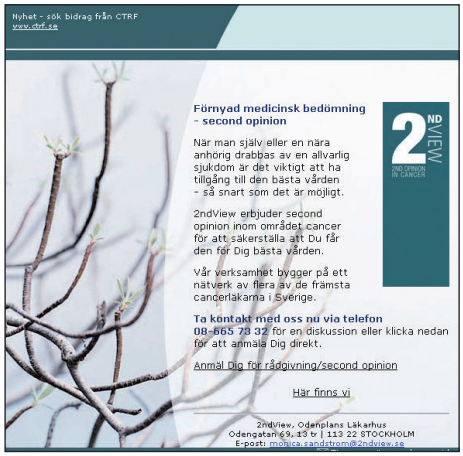
Vinod Joshi, a restorative dental specialist who runs the Mouth Cancer Foundation, another patient group in the UK, says meeting other patients, even in an online forum, can be an important second opinion resource. "They can come to us without feeling they are jeopardising the treatment they have been offered," he says. The fear that many have about 'upsetting'

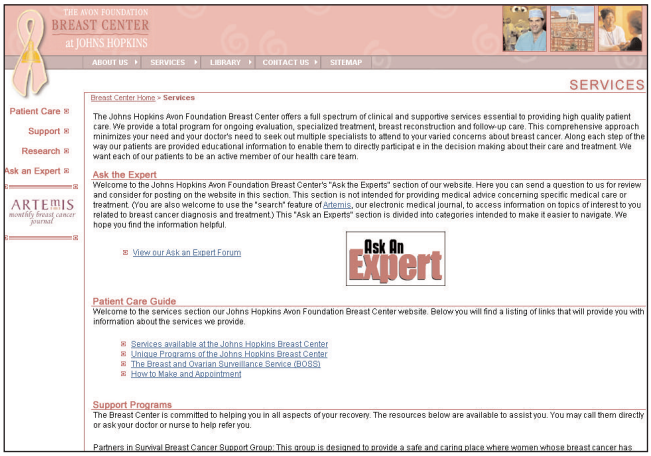
SECOND OPINION PROJECT

A project in Germany is aiming to iron out the differences in outcomes for testicular cancer that are still being seen despite long-established standard care guidelines. A network of 20 second-opinion centres has been established by the German Testicular Cancer Study Group in conjunction with a health insurer. The centres receive patient data and the treatment suggestion from the original doctor, and then recommend therapy according to evidence-based guidelines. The project will follow up patients after two years; it will focus on recurrence-free survival data and will compare intended, recommended and actual therapy.

Mark Schrader, assistant medical director in the oncology unit at Berlin's Charité hospital, is coordinating the data management. "The problem with guidelines is that no one reads them," he says. "We have seen a lot of issues, particularly in some regions and small towns, with diagnostic work-up, therapy and surgery. Now patients and doctors have an easy way to consult specialists at multidisciplinary centres. It is all done by software and e-mail." Some 200 referrals have already been made.

The project has not been without problems. "The health insurer is so far only paying for five of the centres, the others are doing it for free," says Schrader. "But the main problem is the urologists – they are worried that other experts will get all their best patients and they will earn less money." The head of the German Urological Association has been particularly critical, adds Schrader. "There has been an unbelievable amount of tension on this project," he says.





Searching for certainty. Websites like these offer varying levels of information, including extensive lists of FAQs, e-mail response services and even contacts for telephone or full face-to-face consultations

their doctor should not be underestimated; Baird makes the point that unless actively encouraged, people can be very reluctant to seek another opinion. Joshi notes that it is not easy in the UK to be referred to a multidisciplinary centre outside of a patient's home region, or for patients to discover that treatment modalities may differ fairly subtly, say in the radiation fractions given. "These decisions can be affected by finance," he comments. He also feels strongly that oncologists should be open about drug treatments that are not funded in one area – such as cetuximab, which is available for head and neck cancer in Scotland but not yet in England. "It is better than not saying anything about it at all."

From the oncologist's perspective, Vigneri notes that patients need to bear responsibility too. "I have no problem with people seeking alternative opinions, but some go to places that are not well qualified and get answers they like better." The sheer volume of work that referrals can generate is also an obstacle. "Doctors need to prepare an extensive letter detailing the clinical situation of the patient. This material also needs to be translated into English and coupled with copies of the necessary laboratory and radiological exams carried out to evaluate the patient."

If they do go to a centre that is not highly qualified and internationally recognised, "the end result might be confusing, unreliable advice with consequent conflicts between the patient, their family, and the different oncologists involved." Vigneri has also come across patients who have had surgery and, told they also need chemotherapy, delay treatment too long while they 'shop around'.

Another concern he has is when patients fail to seek a second opinion before enrolling on clinical trials, and then drop out. "This can be a huge waste of time for an oncologist."

Quality of life

Schultze at Kiel feels that a key issue that patients don't ask about enough is the consequences of treatment and quality of life. "These questions are not raised much by patients," he says. "For example, prostate cancer is presently a problem, as we are in a phase where we have to make up our mind if someone needs treatment at all, and if so, what treatment to give. And we need to encourage more second opinions on quality of life in palliative care for conditions such as inoperable lung tumours and head and neck cancers where you can apply very harmful, aggressive treatments, but at what price?

"Doctors often decide on a course of treatment easily, but we do not see the burden we are bringing to the patient – for us it is our surgery, for the patient it is the rest of his life."

It is a point strongly endorsed by Joshi. "Rehabilitation is an area that is not sufficiently addressed," he says, noting that, unlike some other cancer treatments, surgery for mouth cancer can be socially disfiguring and can create great functional difficulties. Surgeons, he

The fear that many have about 'upsetting' their doctor should not be underestimated

"For us it is our surgery, for the patient it is the rest of his life"

says, may opt to perform a procedure that is more comfortable for them than the patient, and there are major choices that can be made – such as restoring a hole in the mouth with a prosthesis, or surgically, which can make other restorative work much harder.

"Part of getting a second opinion should include speaking to a patient who has had that treatment and be comforted that people do get through it despite the disabilities. Suppose you have surgery to your mouth, and the surgeon says you should have a feeding tube to your stomach. Some people fear this additional treatment – the second opinion they need is from another patient who may tell them that without it you can't eat, you lose weight and it's the only thing that kept them alive."

A second opinion could also extend to others specialists who are often not part of the 'loop' in the early days of treatment, such as gastroenterologists, who may be able to provide information on the chances of radiation damage to the bowel and subsequent lifestyle issues. Even if there is no alternative treatment, there could then be continuity of care for a patient group that currently receives little attention.

Like many issues in cancer, much opportunity lies in the multidisciplinary team. Paolo Vigneri says it is not uncommon where he works now in Sicily to be visited by patients who have had surgery and had no discussion with a medical oncologist beforehand. Having recently also worked at Bellinzona in Switzerland, which has multidisciplinary tumour boards, he has seen the value of patients meeting both parties prior to any procedure.

One of the strongest appeals for an automatic second opinion comes from the R.A. Bloch Cancer Foundation in the US, founded by Robert Bloch, who survived a terminal diagnosis of lung cancer and went on to live for another 26 years. One day, he was with a medical oncologist who said that he had never in his career treated a cancer patient without a second opinion, because being only human, he could make a mistake – and there is often no second chance. "My conclusion is that any doctor treating a cancer patient without a second opinion is not practising medicine, but trying to play God," says Bloch on the site.

Recognising the importance of multidisciplinary decision making, Bloch's foundation has pushed for patients to be present when their cases are discussed by such teams – to take forward the thoughts of ex-US Supreme Court judge and breast cancer survivor Sandra Day O'Connor in a speech to the National Coalition for Cancer Survivorship back in 1994. "Let me tell you my dream... to have a consultation with all the experts available at the same time, who've already looked at these things, they've looked at everything, and they are all in the same room, and they are there to help you reach a decision."

Dream may be, but the Bloch site has a list of about 100 institutions in the US that say they will provide a multidisciplinary second opinion 'where doctors representing each discipline which could treat the patient's cancer meet together at the same time with the patient.'

Now that is a gold standard to aspire to.

IN SHORT

- Women, especially breast cancer patients, are among the most likely to seek second opinions, probably because of the many different treatment options for breast cancer and its high visibility in the media.
- Computers networks are obvious second opinion enablers. The European Union's e-Health action plan predicts that by 2008 the majority of European health organisations should have the technical capability to provide online teleconsultation services for second opinions and other needs.
- More than a quarter (29%) of US adults reported that they or a member of their family received a second medical opinion from a doctor in the past five years, according to a 2005 Harris Interactive survey. In 30% of these, the diagnosis differed from the original. Another Harris poll in 2006 found that 36% of US adults never get a second opinion and nearly one in ten (9%) 'rarely or never understand' their diagnosis.
- Australian researchers have found that 'Googling' symptoms on the Internet came up with the right diagnosis in 15 out of 26 cases (reported in the *New England Journal of Medicine*). At Duke University in the US, medical physicists are using a Google-like approach to compare mammograms with the most highly ranked images returned from a database.

Fast and effective?

How will EMEA use its new powers of conditional marketing authorisation?

Anna Wagstaff

EMEA's new system for fast-tracking drugs aims to offer quicker access to promising new therapies without jeopardising essential research. Draft Guidance on the use of the new conditional marketing approval procedure will shortly be published, and patients, professionals and the public are being invited to have their say.

In July, the European Medicines Agency (EMEA) threw a possible lifeline to two groups of patients who have reached the end of the road with conventional drug treatment. EMEA gave conditional approval for the use of sunitinib malate (Sutent) for patients with advanced and/or metastatic renal cell carcinoma (mRCC) where interferon alfa and interleukin-2 therapies have failed. It also granted conditional approval for its use in patients with unresectable and/or metastatic malignant gastrointestinal stromal tumour (GIST) where imatinib mesylate treatment has failed due to resistance or intolerance.

For these patients, the early approval of sunitinib gives some new hope. For everyone with an interest in new therapeutics – as patients, public, health providers or drug developers – this represents the first chance to see how EMEA, which has responsibility for approving all new cancer medicines, intends to use its new powers to grant conditional marketing authorisation (CMA).

The concept of CMA was adopted by the EU in 2004 "in order to meet, in particular, the legitimate expectations of patients and to take account of the increasingly rapid progress of science and therapies." Pressure had been growing from European patients with cancer and other life-threatening diseases who could not understand why they should wait months or years longer than patients in the US for access to drugs that could save, prolong or improve their lives.

There was also a perceived need to update the regulatory procedure to take account of the way drug development has been transformed by progress in molecular imaging. The early stages of traditional drug development (pre-clinical, phase I and phase II) tested whether the drug was safe and effective enough to be worth trying in a large confirmatory (phase III) clinical trial. The regulatory procedure therefore focused on the outcome of the phase III trials.

Now researchers are able to see more about what is happening at molecular level, and the early stages have become a fount of information. Researchers can explore how the drug works, what targets it is hitting, which patients have the target and what dose and schedule should be most effective.

The new procedure, modelled in part on the US 'accelerated approval' procedure, gives EMEA two new powers. The first is to approve drugs for a one-year period, renewable annually, as soon as sponsors show data strong enough to demonstrate a positive benefit–risk balance. This has the potential to reduce the period between a drug going into development and the marketing application being handed to EMEA. (The time EMEA spends assessing the drug, is dealt with by a separate regulation on 'accelerated assessment'.) The second is the power to lay down conditions with some legal standing requiring the sponsors to carry out post-approval studies to clarify certain aspects of the drug – duration of effect, which patients it works best in, what is the optimum dosage, and so on.

The CMA procedure is expected to be widely used for new cancer drugs. In particular, it is likely to be used for drugs that would previously have been

The Agency. Decisions on which new drugs will make it to the EU market and which won't are made here at EMEA's headquarters in Canary Wharf, London

dealt with under 'exceptional circumstances' approvals procedure, for which the criteria are more restrictive.

The implementation regulation (507/2006), which came into force in April 2006, spells out the type of drugs that may be eligible for CMA (see box). It also spells out the basis on which conditional marketing approval can be renewed after the approval year is over.

However, the regulation is remarkably vague when it comes to criteria on which approval should be granted. The first criterion listed under Article 4 says simply that "The risk–benefit balance as defined in Article 1(28a) of Directive 2001/83/EC is positive," that is, any risk relating to the quality, safety or efficacy of the product as regards patients' health or public health. There is not the merest hint of direction about how risks or benefits should be measured.

It is equally vague about what EMEA can ask for in post-approval studies. The regulation mentions only that the holder of a CMA shall be required to complete ongoing studies, or to conduct new studies, with a view to confirming that the risk–benefit balance is positive and providing the comprehensive clinical data referring to safety and efficacy that would normally be required for standard approval.

THE CMA REGULATION

Eligible therapies (article 2)

- Medicinal products aimed at treatment, prevention or diagnosis of seriously debilitating or life-threatening diseases
- Medicinal products to be used in response to public health emergencies
- 'Orphan' medicinal products for rare diseases

Requirements (article 4)

- Positive risk–benefit balance
- Applicant 'likely' to be able to provide comprehensive data post-approval
- Meets unmet needs
- Early approval of benefit to public health on balance

Renewal (article 6)

- Annual renewal
- Risk–benefit balance to be confirmed, meeting CMA obligations

CMA versus Exceptional Circumstances

Approval under exceptional circumstance can only be applied to drugs where it is deemed impossible ever to collect comprehensive data due to rarity or because it is contrary to medical ethics, or the state of scientific knowledge does not allow such data to be collected. The CMA procedure can be used to give early approval to drugs that can show a positive benefit–risk before the comprehensive data set is available, leaving the supplementary clinical data to come later.

Collection of further pharmacovigilance data can also be required.

Quite how this will translate into practice, and the implications for cancer patients, drug developers, and health providers, depend heavily on how these broad-brush requirements are interpreted.

Will there have to be data from a randomised trial? Will the new therapy need to be compared against best care or a placebo? Could it be enough just to show the response in a single-arm trial? Will drug sponsors have to show which target is being hit, and identify the group of patients who are most likely to respond? How many patients will be required for data on efficacy or safety? Will the drug need to show clinical benefit on survival or symptoms? If 'surrogate endpoints' are used (see box), what level of certainty will be required to show that the surrogate is reasonably likely to predict clinical benefit?

There are also questions about post-approval study requirements. What sort of studies will be asked for, and what will happen if a drug sponsor does not fully comply? Will CMA be withdrawn if the post-approval obligations are not fulfilled?

Three main stakeholder groups will be affected by the way EMEA addresses these questions: patients who have run out of other options, drug developers, and the general public.

The patient – a lifeline

What matters to patients is access to effective drugs as quickly as possible, through 'conditional' approval or any other route, such as participation in clinical trials or compassionate use programmes. Safety is not the primary issue for many of them, who are facing the prospect of death or a very impaired quality of life anyway. They would probably set the risk–benefit hurdle fairly low. This translates into accepting less demanding trial designs, and allowing benefit to be measured in terms, for instance, of tumour shrinkage, which tends to be quicker to measure, but may not accurately reflect true or sustained benefit in terms of survival or quality of life.

Precise identification of the target group will not be a major priority. If the data indicate that the drug is effective in one in ten patients with a given indication, most patients would at least like the option of 'giving it a go', particularly if side-effects appear encouraging. Patients are likely to be very supportive of any studies that could throw further light on how and in whom the drug in question works best – but not at the cost of delaying access.

The industry – quicker returns

The second group of stakeholders are the sponsors of experimental drugs, principally pharmaceutical companies. Kapil Dhingra, vice president of the oncology division at Roche, speaking at the European Society for Medical Oncology (ESMO) last October, welcomed the new approval, and said the approval of sunitinib was "a good start". He characterised the main advantages for the industry as early certainty about a drug's launch, and early return on investment.

The July 2005 issue of *Regulatory Rapporteur* said that early approval may be particularly important for biotech companies, which play a key role in developing molecularly targeted therapies but don't always have the resources to conduct long and expensive phase III trials.

Financially, then, this would be a good deal for the industry, good for shareholders, and good for the rest of us if lower costs stimulate innovative research or result in lower prices and more thorough research into new drugs.

From the developer's point of view, the guiding principle on approval is 'the earlier the better'. In general, they will be looking for the number of patients and the length of time required to prove efficacy and safety to be set somewhere at the lower end of the scale, and they will want EMEA to adopt less rigorous measures of efficacy. Rather than having to show survival data, which can take a long time to collect, the industry would prefer CMA to be granted on data about response rate (tumour shrinkage), time

SURROGATE ENDPOINTS

Surrogate endpoints are measurable variables deemed likely to predict clinically meaningful endpoints such as longer survival or reduced symptoms. They can be quicker to evaluate than clinical endpoints, but their predictive powers are not very accurate. CMA is likely to rely heavily on data from surrogate endpoints, with the option of requesting post-approval studies to see how this translates to clinical endpoints.

Traditionally, a limited group of surrogate markers have been accepted on a case-by-case basis, including response rate (tumour shrinkage) and time to progression or progression-free survival. These may, in the future, be extended to include functional imaging, such as measures of apoptosis/antiproliferative effects, and also pharmocodynamic biomarkers such as PSA as a marker for prostate cancer or CA 125 for ovarian cancer. However, statistical validation of these sorts of surrogate biomarkers is proving very difficult.

Response rate was the basis for 30 out of 48 approvals, but this translated very poorly into survival benefit

to progression (how long the drug keeps the disease at bay), functional imaging (imaging levels of cell death or cell proliferation) or biological markers of efficacy.

The industry also has a view on post-approval studies. Once a new drug as been approved, pharmaceutical companies will want to move on. They have little interest in tying up resources in research that may offer little financial benefit and may even diminish the market as research identifies which subgroups of patients respond best.

There are also ethical and logistical problems to conducting such studies after a drug has reached the market. Patients often join a trial of an experimental drug in the hope of being randomised to receive the new treatment. Once the drug is on the market, joining a randomised trial actually decreases their chances of getting the drug which they could otherwise have on prescription.

At the ESMO meeting, Dhingra stressed the need to have a very clear definition of the clinical objectives, scope and timelines for post-approval studies, and said that EMEA needed to take account of what was feasible.

The public – effective treatment

As a third stakeholder, what the general public wants amounts to efficacy and efficiency. As potential patients, they want a system that encourages drug developers to find effective therapies targeted precisely at the specific malignant phenotype driving the cancer. They want the treatments that can be delivered in the most effective schedule, dose, combination, and method of administration, and they don't want to take therapies that might be of no benefit for their particular disease, but might have nasty side-effects.

As tax, medical insurance or treatment payers, the public does not want to foot the bill for prescribing an increasing number of highly expensive drugs to broad populations of patients if only a minority are likely to benefit, and if clinicians do not have the information to use them to greatest effect.

A group of researchers at the Mario Negri Pharmacology Research Institute, in Milan, argue that EMEA and its US counterpart, the FDA, have "a major role in improving public health, as they fall between clinical trials and (public) health care" and that "drugs must be rapidly released for patients who need them, but not at the expense of adequate knowledge about the benefit of the drugs."

Their paper, published in the *British Journal of Cancer* (vol 93, pp504–509), analyses the basis on which EMEA has approved drugs for solid cancers over the 10 years since centralised marketing was introduced in 1995, and argues for raising the standard of proof, particularly for clinical benefit.

Looking only at applications for new drugs or for extended indications for therapies for solid tumours, they point out that response rate (usually given as the percentage of patients whose tumours shrunk by at least 50%) was used as the primary basis for granting 30 out of 48 approvals, but that, in cases where data were available, this translated very poorly into survival benefit. In 13 cases for which survival data were also given, the benefit ranged from 0 to 3.7 months, with mean and median benefit of 1.5 and 1.2 months.

The authors also point out that 30% of approvals were given on the basis of single-arm trials, despite the advice in EMEA's own Note for Guidance 'Evaluation of anticancer medicinal products in man' (2002). This says that randomised comparative trials are normally always required, with no comparative trials being considered acceptable only in the case of pretreated patients when no established regimens exist.

In the US, more than 90% of post-approval study commitments remained unfulfilled according to a 2005 FDA report. The Mario Negri researchers conclude that the public interest is best served by keeping the efficacy hurdle higher, rather than relying on post-approval studies to come up with more robust data.

They argue that EMEA should insist on seeing overall survival data in combination with formal assessments of symptom control or quality of life. These assume greater significance given the rather small median survival benefit of 1.2 months offered by drugs for solid tumours approved over the past 10 years.

On the question of trial design, they make the case that there should be a requirement for phase II randomised trials, with patients randomised to the new drug or to best available care. They also argue that phase III comparative trials should be the norm for the approval of new anticancer drugs, with phase II studies only accepted in exceptional cases, when there is really outstanding, unprecedented or unexpected activity.

EMEA is moving away from the 'gatekeeper' model towards more constructive communication

To ensure that the regulatory process takes into account the needs of patients for whom experimental drugs may be their only hope, the researchers suggest greater patient involvement in the EMEA evaluation process to help identify which drugs really need fast-track designation. They also emphasise the importance of effective information to spell out to patients the risks of a partially proven therapy.

Selective approval

Current understanding about the complexity of cancer and of mechanisms of action and of resistance to drugs suggests that the disappointing clinical benefit shown by many drugs in the above study may indicate not that the drugs are ineffective, but that they are effective in only a small part of the population they were tested in. The worry is that the great promise of the era of individually targeted treatments may never be realised if therapies are marketed early, with insufficient information about selection of the target group, especially if nobody takes responsibility for the necessary post-approval work.

The experience with gefitinib (Iressa) for non-small-cell cancer is often cited to illustrate the problems. Rejected by EMEA because of lack of survival impact in an unselected population, the drug has since been found to be effective in a certain very specific subgroup. Makers AstraZeneca claim it would have been almost impossible to identify this target group had the drug not been on the market, and thus widely used, in the US and Japan. Many voices from the national regulatory agencies, however, believe that companies seeking approval for a targeted drug should not expect to get approval for its use in an unselected population.

A key paper published in the *New England Journal of Medicine* two years ago (Roberts and Chabner, vol 351, pp501–505) argued that it may be unrealistic to expect pharmaceutical companies to carry out these studies, as they can be very complex, time-consuming and are likely, at least in the short term, to diminish the market for their drugs.

For the US, they proposed a mechanism for 'selective approval' whereby early approval could be granted, "only if the sponsor has initiated studies to identify subgroups of patients who are likely to have responses." The regulators and drug sponsors would reach agreement over how the studies could be concluded, with an option of forming a partnership with a public body such as the US National Cancer Institute or an academic centre, with a certain percentage of profits from the early marketing of the drug set aside to fund this research.

Sadly, Europe has no equivalent of the NCI. However, there are many international cooperative groups, as well as the European Organisation for Research and Treatment of Cancer or the French National Cancer Institute, INCa, which recently launched a post-approval trial (PHARE) to find out more about the best way to use adjuvant trastuzumab (Herceptin).

The view from EMEA

Faced with these potentially conflicting pressures from patients with unmet need, from the industry and from the public interest, how is EMEA going to implement the CMA regulation? So far, the approval of sunitinib is all that anyone has to go on, because EMEA is still in the process of drawing up draft Notes for Guidance. However, Francesco Pignatti, Scientific Administrator at EMEA, agreed to share his personal views with *CancerWorld*.

Pignatti stresses that CMA requires proof of a positive risk–benefit balance. "Some people understand CMA as putting drugs on the market without knowing their efficacy, and that is not what is meant by conditional approval. I think that even for CMA it is crucial that a drug is only ever put on the market when EMEA's scientific committee has judged that, based on the evidence available, the benefit–risk balance is positive The draft of the regulation started off saying the benefit–risk is 'presumed positive'. Now that word has gone from the final legislation."

He accepts, however, that, despite being as objective as possible, assessing the risk–benefit balance is not an exact science. "One needs to express value judgements on multidimensional concepts – benefits, risks – each estimated with variable degrees of uncertainty. Without comprehensive clinical data, as for CMA, the real challenge is to identify situations where it is still possible to conclude on a positive benefit–risk balance."

Given the subjective nature of the judgement, patients will need to have a strong voice in the regulatory process to ensure their voice is heard. Traditionally, Europe has lagged far behind the US in this respect, but EMEA has been trying hard to catch up. A Working Group with Patients and

Consumers Organisations now enables these groups to have a formal consultative role. Though for some patients this falls far short of the partnership they would like, the European Cancer Patient Coalition and other patient groups have welcomed the move.

Pignatti sees a cultural shift away from the 'gatekeeper' model towards a constructive communication among stakeholders more appropriate to today's rapid progress of basic science and cancer therapies. "In this context, CMA makes a lot of sense – it weighs the need for a comprehensive clinical development with high unmet need and public health interest in getting beneficial drugs quickly to patients in desperate need."

Pignatti envisages the use of surrogate endpoints so long as they are considered "reasonably likely" to predict an effect on a clinical endpoint such as survival, and so long as the effect on the surrogate is great enough. "There are some surrogates where the prediction is sufficiently high that if the effect is big enough, and looking at all the supportive evidence, you know that it will be very likely also to mean something in terms of clinical benefit."

Minimum data sets

Asked about what he would envisage to be the minimum specifications in terms of trial size and design required to grant approval, Pignatti said, "It is not about the minimum. It is about giving yourself the chance in a comprehensive development of deciding at which point there could be sufficient evidence to go for approval."

He is cautious about spelling things out in detail, because there are so many possible variables: the rarity of the indication, the level of toxicity, whether alternative therapies are currently available, whether the drug shows dramatic or less-pronounced activity and so on. He recognises, however, that the window of opportunity for performing a randomised study in a certain indication may only exist before approval, and he ventures some general comments.

"To aim for early approval, one should randomise early in the clinical development. Preference should be given to study designs and endpoints that can capture convincingly a clinical benefit as early as possible. In the standard approach we would certainly say 'do a randomised trial, and if appropriate plan for an interim analysis when you have a sufficient number of patients when it is meaningful to draw some conclusions, in case the treatment effect is much larger than initially expected.'

"I would not recommend a strategy focussing on single-arm studies for approval. However, if one happens to observe a dramatic effect in a single-arm study, it may be that randomised trials are no longer needed. But this should be the exception, and there may be

THE SUNITINIB PRECEDENT

Sunitinib is the only drug so far approved by CMA.

Trial design

The demonstration of efficacy in patients with metastatic renal cell carcinoma (mRCC) who were refractory to prior cytokine therapy with interleukin-2 or interferon α was based on the proportion of patients achieving an objective response observed in two single-arm studies. The studies were conducted in a homogenous group of progressive patients with a predictable outcome of the disease.

Results

The estimated proportion of responders was 36.5% (95% CI 24.7%–49.6%) and 35.8% (95% CI 26.8%–45.7%).

EMEA's opinion

EMEA's Committee for the Evaluation of Human Medicinal Products (CHMP) considered the effect in terms of tumour shrinkage to be unprecedented, even with the most active available agents in a non-refractory population for which response rates in the order of 5 to 15% have been reported. They found that the efficacy results provided sufficient confidence to believe that treatment with sunitinib would translate into some effect in terms of progression-free survival or overall survival in patients who have failed prior cytokine-based treatment, although they were unable to assess the exact size of the effect on these clinical endpoints.

Post-approval studies

At the time of approval, the CHMP considered that data from an ongoing randomised trial of sunitinib as a first-line treatment in mRCC patients could help to confirm that treatment with the drug is associated with an effect on important clinical endpoints. Although the ongoing trial involved an active control and patients in an earlier stage of treatment, based on pharmacological and biological grounds, the demonstration of a favourable effect as a first-line treatment would be considered relevant also for patients with mRCC who have failed prior cytokine-based treatment. This would confirm the existence of an effect in terms of relevant clinical endpoints even if the precise magnitude of this effect would not be known.

Upgrading to full approval

The randomised trial has now been completed and in October EMEA's Committee for Medicinal Products for Human Use recommended that sunitinib's CMA should be upgraded to full approval, with the approval being extended to cover first-line use in mRCC patients.

No drug approved via CMA would be withdrawn purely because the conditions were not fulfilled

different perceptions about what constitutes a 'dramatic' effect. Indeed in our experience, lack of an adequately randomised controlled trial has been an important reason for rejection."

A look at EMEA's track record, however, shows that 16 (44%) of the 38 oncology new drug applications that were granted marketing authorisation in the last 10 years were approved on the basis of single-arm trials, and Pignatti acknowledges that this is an issue of concern in some quarters.

In the case of sunitinib, approval was based on the results of two single-arm trials. There were, however, early supportive data from an ongoing randomised trial in a different category of patients. Completion of that randomised trial was one of the conditions EMEA set for giving sunitinib conditional marketing approval.

A POWERFUL TOOL

The power to set these sorts of conditions is something new for EMEA. How that power will be used is one of the big question marks relating to the new approval procedure.

Pignatti points to the second criterion under the Requirements section of the implementation regulation, that it must be "likely that the applicant will be in a position to provide the comprehensive clinical data," (post-approval), and he argues that getting agreement with the drug sponsors over what studies are feasible and appropriate will be key to overcoming compliance problems.

He is clear that there will be strict limits to what post-approval studies are asked for. "You shouldn't be imposing more requirements than necessary. So if for instance we have a drug that works in refractory disease, and then we are interested in knowing whether it would also work early on, that should not really be a CMA type of question. But if we have some uncertainty in the indication in which it is currently approved, and we think we could extrapolate information from an earlier indication to reduce that uncertainty, then we can ask that question."

This is what was done in the case of sunitinib (see box, p27).

Regulations are being drafted that will allow EMEA to impose fines for non-compliance. Doubts have been expressed in some quarters over whether financial penalties are an appropriate way to deal with issues like clinical trials, and time will tell how much use EMEA will make of these powers. Pignatti is clear, however, that although approval is conditional on the required studies being carried out, no drug approved via CMA (i.e. positive benefit–risk had been established) would be withdrawn from the market purely because the conditions were not fulfilled.

The key, he believes, is to ensure that patients and prescribers understand the implications if a therapy they are using has conditional rather than full marketing authorisation.

In the case of sunitinib, the information says: "This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine, in particular in the treatment of kidney cancer. Sutent [sunitinib] has shown to shrink the tumour. However, more information is awaited on the duration of this effect. The European Medicines Agency (EMEA) will review new information on the medicine every year and this leaflet will be updated as necessary."

Pignatti believes that this kind of clear information to physicians and patients will be an incentive for companies to finish the required post-approval studies to upgrade to standard approval.

Is it realistic to rely on clear communications to make the regulatory system work, or will EMEA's voice be drowned out by the heavy guns of pharma advertising, at least among the non-specialists who are still responsible for prescribing cancer drugs in many parts of Europe? Should CMA be used sparingly to avoid non-compliance, and if so, what of the patients who need quick access to new therapies? Once positive risk–benefit has been proved to the standard required for CMA, has EMEA any business demanding any further data? But if they don't, then who has responsibility for carrying out the trials needed to find out how best to use the drugs and in whom?

Clinicians, patients, health administrators, policy makers and members of the public who have an interest in the new drug approval regulations should look out for the draft Notes for Guidance document scheduled to be published on the EMEA website www.emea.eu.int. It will be a consultation document, and EMEA wants your views.

From plan to practice

The French Cancer plan of 2003 raised expectations among the public and patients. This article, which looks at how a key measure is being implemented in practice, was one of several stories that earned **Paul Benkimoun** recognition in the 2006 ESO Best Reporter Awards.

Bad news will always be bad news, but the way it is told makes a big difference. Throughout the year, some 37 pilot schemes running in 58 institutions have been trying out a novel way of breaking the news of a cancer diagnosis that was developed in conjunction with patients. It aims to improve the conditions under which patients are notified of their condition and told about the treatment they will be given. As the pilots started gradually, full results are yet to be obtained. And the pilot schemes are set to be extended to all the sites treating cancer during the second half of the year.

In 1999, the *White Book* of the National Anti-Cancer League carried testimonies from people who were disgusted by the off-hand or brutal manner with which they were told of their illness. A symbol of the battle of patients, the improvement of the conditions under which news of the diagnosis is notified, was number 40 in a list of 70 measures of the Cancer Plan, launched in March 2003 by [President] Jacques Chirac.

A budget of 3.2 million euros was allocated, amongst other things, to pay for the creation of new nursing jobs. Another 15 million euros were set aside to extend the scheme in 2005, a sum that will have to be revised in 2006. The project was geared up to include 25,000 to 30,000 patients throughout the year. Ten months into the trial, some 15,000 people have taken part in the system, which is piloted by the National Cancer Institute in tandem with the National Anti-Cancer League and the Directorate of Hospitalisation and Care Management.

"You don't know anything"

The trial relates to the notification of the diagnosis, or its confirmation, but also to "the proposal for a treatment plan" decided at a multidisciplinary meeting, and to "the provision of a team of carers" including a psychologist and a social worker, as laid down in the specifications.

Patients can find familiar contacts within the system, and in the case of the reporting nurse, somebody who is more accessible than a doctor.

"The consultation with the nurse is a sort of 'emotional catharsis' for the patient and a time when medical terms will be translated into less academic language than is used by a doctor," said Professor Henri Pujol, president of the National Anti-Cancer League. "We feel physically, and also intellectually, diminished. We don't know anything when faced with the doctor, the one who knows," commented Henri Gontier, a member of the patients' committee at the Institut Paoli-Calmettes (IPC) in Marseilles.

"In the case of tumours whose location is highly symbolic, such as the brain, you cannot just say straight out: You have a brain tumour," explains Dr Olivier Chinot, of the neuro-oncology unit at the Timone University Hospital, in Marseilles, who is highly involved with paramedical staff in these trials. "Often patients do not ask the prognosis."

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FRANCE-SOCIÉTÉ

SANTÉ

Un dispositif d'annonce des cancers devrait être généralisé

Le Monde

Watchdog. Articles like this, which explore how far commitments to cancer patients are actually being translated into better services for all, put pressure on health services to deliver, and let patients and their families know what they have the right to expect

"They or their family ask us," elaborates Soazic Duval, a nurse in the same department. "Bearing in mind the loss of independence that results from brain cancer, we have to take into account from the start the friends and family of these patients, who are often young," adds Bruno Tivoli, the hospital executive who implemented the new system at la Timone teaching hospital.

Patients are also more likely to speak to the nurse about matters deemed 'delicate', or too banal to raise with the doctor. It is at this point that many patients discover that, in addition to causing them to lose hair from their head, chemotherapy often causes the loss of pubic hair. The matter of wigs is frequently broached.

As a by-product of these pilot schemes on the notification of cancer diagnoses, doctors have learned the value of information gathered by paramedic staff. "We had not sufficiently questioned the ambulance drivers, who take patients home, about the sickness caused by chemotherapy," acknowledges Dr Jacques Camerlo, trial coordinator at the IPC.

"A TURNING POINT"

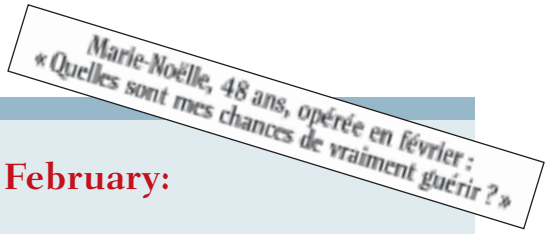
A notification system also calls for a *rapprochement* between hospital doctors and their colleagues on the outside. The general practitioner (GP) is, in fact, involved in informing the patient of the diagnosis. "A general practitioner from Marseilles told me: 'When I refer a patient to the Institut Paoli-Calmettes [specialist cancer centre], don't you think that I have held a patient notification consultation?'," says Dr Camerlo. "The GP needs to be informed very quickly," urges Dr Christine Bara, from the National Cancer Institute, who states that three-quarters of patients go to see their GP immediately after the notification consultation.

The pilots of the project know that making the scheme universal will not be simple. Even in Marseilles, often cited as an exemplary case, things have not always been simple. "Some doctors from la Timone University Hospital have had the honesty to say that they did not want to take part. Some give their agreement, but only send us one follow-up sheet per month," says Professor Pierre-Henri Juin, who has been coordinating the experiment there for a year.

It is clear that there is a need "to proceed gently and with flexibility", as Christine Bara says. "It is a question of a qualitative approach. We must avoid a purely administrative application of the system," she adds. If you try to act on the frequent request from patients that notification consultations should no longer be held on Friday, leaving them on their own throughout the weekend, then you will probably have to take into account the problem of availability of doctors.

Flexibility is required, but also determination. "Patients have worked on this for four or five years. Therefore they are expecting changes. This will be a turning point in the relations between doctors and patients," predicts Professor Pujol. He agrees with Dr Bara that further consideration needs to be given to four areas: paramedical consultation, the interaction between the local community and the hospital, the identification of psychological and social needs, and the personalised treatment plan.

Some practitioners look further ahead. "We will undoubtedly have to come up with an end-of-treatment system, as patients often collapse psychologically when they are no longer cared for as closely as during the treatment stage," observes Professor Dominique Maraninchi, director of the IPC and chairman of the science board of the National Anti-Cancer Institute.



Marie-Noëlle, 48 years of age, operated on in February:

"What are my chances?"

She knew it as she pushed open the door to her GP's office. In fact, she knew it when she felt a lump as she examined her breasts one day in September 2004. Marie-Noëlle M., 48 years of age, was operated for breast cancer on February 4th, at Martigues Hospital.

One month later, Marie-Noëlle pushes open the door of the consulting room at the Institut Paoli-Calmettes in Marseilles, a regional anti-cancer centre, where Jacques Camerlo is waiting for her. This doctor coordinates the local pilot programme for the new cancer notification system. "We are going to go back over everything and reformulate everything," he announces.

Before starting to examine her, Jacques Camerlo talks to her about her illness: "Breast cancer is a common disease which affects one in nine women. It can be cured and removed if various stages and treatments are complied with." Marie-Noëlle interrupts the stream of explanations and details: "No-one ever explained that to me," or "that's not much fun," when the subject of chemotherapy is broached.

She has clearly thought about her illness a great deal. Some questions are very specific: "*Am I going to have a wig?*" Other questions are more fundamental: "What are my chances of really getting better?"

Jacques Camerlo answers, without beating about the bush: "The treatment that you will have will make it possible to get rid of the disease. We will have done everything in order for you not to need to come back to see us. You will have more than a 70% to 80% chance of it not coming back."

Marie-Noëlle's two sons, aged 27 and 25, are very well-informed, as is her husband. "I want my children to continue with their lives as normal," she says. "I don't want them to be watching over me too much."

A little later, she confides: "I am a worrier by nature, especially about others." Jacques Camerlo tells her: "Take care of yourself first. Your day-to-day, social and emotional life must continue normally. The side-effects of the treatment are temporary and reversible."

" Call me"

The doctor describes the different stages of the six-month treatment plan awaiting Marie-Noëlle – chemotherapy sessions every three weeks, then daily radiotherapy for four to six weeks. He gives her the names of the doctors who will be involved. He then tells her of the various possible side-effects of the treatment, and the symptoms that she should watch out for – particularly any signs of a fever, as the treatment will severely compromise Marie-Noëlle's immune system. "I am going to need a computer to remember all that," she quips.

Having summarised her forthcoming phases of treatment in a document entitled "Theoretical treatment plan", which he gives her, and having dictated in her presence a letter to the doctor who referred her, Jacques Camerlo introduces Marie-Noëlle to Jean-François Cailhot.

Cailhot, a nurse, coordinates the care of women being treated for breast cancer at the Institut Paoli-Calmettes. "Whatever the problem, call me, I will put you in contact with the people you need," he says, giving her his card.

The nurse asks Marie-Noëlle what is the main problem that she is concerned about. "Losing my hair", she answers immediately, adding: "I have already found out about wigs." He tells her that her hair will start to fall out at the start of the second week of treatment, and mentions the various models of wig, reminding her that a hairdresser is available at the Institute.

Next subject: side-effects. His advice relates to everyday life: "You will be given drugs, but we cannot predict how you will react. Try not to plan too many activities during the three days following the chemotherapy session," he stresses.

Mentioning the possibility of a fever, he recommends: "Somebody must be available to bring you here 24 hours a day, 7 days a week. You must keep the phone number of a taxi or an ambulance on you and a packed suitcase. It doesn't happen often, but …"

He reminds Marie-Noëlle that a psychologist and a social worker are at her disposal, and that she does not have to pay for her transport to the Institute for the chemotherapy sessions. He concludes by giving her an information leaflet on breast cancer.

Feeling a mixture of resignation and satisfaction, following this initial contact with those who are going to steer her through her six months of treatment, Marie-Noëlle prepares to return home. She will soon be back.

Tackling cancer the Tunisian way

Jim Boumelha

Farhat Ben Ayed played a key role in building Tunisia's cancer services, armed with little more than a solid education, a sense of duty and a remarkable talent for motivating others. Fighting cancer, he believes, is a question of citizenship and solidarity, and limited resources cannot be allowed to stand in the way.

Rising life expectancy, swift urbanisation and major changes in dietary habits all preface an inexorable rise in cancer. Tunisia fits this description. With 10,000 new cases a year, this small country is on a rising cancer curve. With the limited resources of a country in transition, it is about to cross its Rubicon.

Unlike many countries moulded by similar historical events (the French occupation ended 50 years ago), Tunisia has no army to speak of, investing its human capital in education and health. Tunisia's health budget tops 8% of national spending.

This is perhaps one reason why Professor Farhat Ben Ayed, the father of Tunisian oncology, is in an almost permanent state of reflection on the meaning of the fight against cancer, in particular with the cost "of what has already been done and what we have failed to accomplish". It is also a reason why equality of treatment has become almost an obsession. His commitment to cancer patients is a commitment to people's rights. "The fight against cancer for me is not just a question of specialists, but most crucially an issue of citizenship."

In identifying risks and setting out strategies to improve prevention and early detection, to develop new therapies and to improve social rehabilitation, Ben Ayed is careful not to follow blindly the example of Europe. "We have different priorities. Our top priority is the fight to reduce tobacco consumption because lung cancer is the number one killer in our country. It cannot be breast cancer detection, where we are hampered by the fact that it is most prevalent among the under 35s, making it difficult to screen. With our foreign friends we discuss continuously what kind of projects we need to advance, what can or can't be achieved and, most importantly, what can we do to affect the maximum of people."

With 25% of cancer patients coming forward at such a late stage that curative treatment is no longer possible, it has been necessary to develop psychosocial support for individuals and families living with cancer. In the Tunisian context, oncologists have also to grapple with the

notion that cancer is a punishment. The first and most crucial action has been to focus on demystifying cancer which remains a taboo subject. Tunisian families live in such a fear of the disease that they cannot bring themselves to call it by its name.

"We are struggling to convince families that cancer is just like any other disease. In the present state of thinking, it does not just affect the individual, but has an impact on the family as a whole. The whole family is weakened; their social status goes down, acute depression follows."

Patients are developing higher expectations, both in terms of which cancers can be cured and what happens to patients when a cure is not possible. Palliative care and the concept of a hospital without pain have become the norm. Thanks to a monopoly on importation of drugs, the state-owned Pharmacie Centrale makes most drugs, including all types of opiates, widely available, putting Tunisia ahead of many other Arab countries in its ability to deliver pain relief.

Although Pharmacie Centrale imports most of the newer cancer drugs, Ben Ayed stresses that much of the progress, in particular in paediatric oncology, has been achieved by making better use of old drugs. The top priority must remain the overall interest of all patients and not just a privileged few, he says. Tunisia has not the means to gamble precious resources on a treatment that can only be used for 8% of patients.

The strong arm of the state makes a difference for both drugs and infrastructure – most hospitals are now equipped with scanners and there are six MRI machines in Tunis alone – but there is an acute need to further develop the national cancer plan, so that it does not remain the sole property of the cancer specialist. Ben Ayed argues that the involvement of citizens is a major missing component.

"Top priority must remain the overall interest of all patients, not just a privileged few"

Farhat Ben Ayed talking to patients at the Eddar Hospice in Tunis

Unlike oil-rich countries in the Arab world, Tunisia has no petrodollar reserves. Pioneers like Ben Ayed organise the fight against cancer with few resources, armed with a solid education, a sense of duty and exceptional organisational wizardry in the art of motivating others. Partly as a result, Tunisian oncology punches far above its weight.

Ben Ayed learned two things from his childhood – he assimilated from his home island of Djerba the art of being a hard taskmaster and, from his parents, a sense of giving without expecting anything in return.

He set out to study philosophy but converted to medicine once he saw his older brother in action – Si Hassouna was to become the first Tunisian nephrologist. Ben Ayed enrolled at the medical school in Montpellier, France, and conducted his postgraduate diploma at Tunis and the Gustave-Roussy Institute, in Villejuif, France.

Ben Ayed came home with a mission – to help build the foundation of medical oncology in Tunisia. He worked to strengthen the first and second pillars of this work, cooperation with the outside world and the Tunisian Cancer Institute (now called Salah Azaiez). The third pillar, the creation of an association to fight cancer, is where he has concentrated his efforts for the last 20 years.

Over two millennia, Tunisia has been invaded by Vandals, Phoenicians, Greeks, Romans and Arabs. In modern times, it became a province of the Ottoman Empire and later a French colony. It is not surprising to find a tradition of cooperating with others profoundly ingrained in the country's psyche and within the scientific community. The French not only left a substantial legacy, but continued to play a major role in training Tunisian oncologists and helping the country develop its infrastructure.

Charles Nicolle, the first doctor to win the Nobel Prize in Medicine while working on African soil (he discovered the transmission agent for typhus), conducted his research from the Pasteur Institute in Tunis.

French oncologists gave the impetus in the late 1960s to creating what was to become the Salah Azaiez Institute, the nerve centre of Tunisian oncology and the first cancer institute in the Arab world.

Ben Ayed shows great respect for the personal commitment of French colleagues. "To be honest it was a generous cooperation. They gave so much and never asked anything in return."

His studies in France arose from a visit by a French team to Tunis during which he met Jean Louis Amiel, a leading oncologist at the Gustave-Roussy Institute, the beginning of a friendship that would last until Amiel died in 1985. "We went on to build an exceptional network of friends, people with an exceptional knowledge. This was the first step for us in building our knowledge of clinical oncology and understanding the founding principles of biological oncology. From there on, there was no going back. I was hooked into medical oncology.

"Many outstanding personalities like Professor Amiel became icons. He often travelled to Tunis as a friend not just as a colleague. And even today, after his death, when confronted with a thorny problem we often try to imagine: what would Professor Amiel do in such a case?"

The mix of professional and friendship ties meant that it was not difficult to involve colleagues from institutes and hospitals all over

France – Marseilles, Rouen, Lyon, Gustave Roussy Institute, St Cloud. A simple phone call was enough to convince them to make the trip. The multidisciplinarity of the Tunisian cancer institute was in large part thanks to this input.

Other countries became involved. The Italians helping to set up screening for cervical cancer and short courses for doctors and interns.

Later, the training of trainers was taken up by the French national anti-cancer league with the help of the UICC. A French NGO, Douleur sans frontières, set up training to show general practitioners how to treat pain. International collaboration is still important. A soon-to-be-published report on the epidemiology of cancer of the larynx organised by the International Agency for Research on Cancer (IARC) brought together researchers from Tunisia, Indonesia, Canada, China and France. Tunisia is also involved in a number of international phase II and III research projects.

Tunisian oncologists also recognise the need to build horizontal links with colleagues from the rest of the Arab world and the African continent. Ben Ayed has been building steps towards lasting cooperation between oncologists from the Maghreb ("the West") – made up of Morocco, Algeria and Tunisia.

"The Maghreb is my top priority. We all received the same French training, which makes it easy for us to work together and communicate. So it's not difficult to knit a web united around common options and joint work.

"Every year there are 70,000 new cases of cancer – 30,000 in each of Morocco and Algeria and 10,000 in Tunisia. We are currently discussing whether all these new cases are receiving an adequate and correct treatment. It would be all too easy to find excuses because of our inadequate resources. But this should not prevent us from researching, for example, the psychosocial context – how to deal with the quality of life in Tunisia and the rest of the Mediterranean region."

Ben Ayed is less optimistic about links with the rest of the Arab world. He argues that the Arab League has the necessary structures to lead the fight against cancer in the region, but says that this is inhibited by rivalries between countries.

Tunisia would like to do more in the way of training for doctors from sub-Saharan Africa. Lack of international recognition for Tunisian diplomas means that there is little incentive for African doctors to do their training here. However, strong links have been built with French-speaking countries in West Africa.

None of this cooperation would have taken shape without the Salah Azaiez Institute as the engine driving the fight against cancer in Tunisia. Since its inception in 1969, the Institute has based its structures, development and day-to-day practices on the Gustave-Roussy Institute, including administration, care and training.

However, the Tunisian approach to cancer treatment and care has evolved from local realities. "Our starting point was to cure every case. We realised very quickly that we could not. This is one reason why developing palliative care became a prime dimension of our work. It is through training specialists in the treatment of pain and in palliative care that we managed to open the door for the training of paediatric oncologists. It has also led to the development of psychosocial support for individuals and families living with cancer."

The Institute has revolutionalised the teaching of cancer at the Tunisian medical faculty. For example, paediatric oncology was not recognised as a specialty at the faculty until it was practiced at the Institute. Today, Tunisian children's hospitals all handle childhood cancers. The Institute also encouraged the publication of high-quality research reports by Tunisian teams

"It would be all too easy to find excuses because of our inadequate resources"

"I admire the Canadians and Irish for their willingness to confront the tobacco lobby"

on child lymphomas, breast cancers and other topics, raising their international profile.

The Institute has influenced other regions of Tunisia – Sfax and Sousse are also developing as major cancer treatment centres. Multidisciplinary treatment, palliative care, psychosocial themes, and research have become central pillars in the fight against breast, colorectal and lung cancer.

Many doctors are still sent abroad to learn new approaches to treatment and care. A few stay away, lured by better wages and prestige. However, most return with a renewed allegiance to their home country and find immense satisfaction in what they are doing. "When 80% of children are cured of cancer, isn't it great to see some of them growing up and becoming doctors or engineers," notes Ben Ayed with a smile.

He believes that an effective fight against cancer rests on a partnership between the public, the private and civic society. "Every person has a role to play. Cancer is a question of solidarity. Everybody should join the fight."

After years of developing medical approaches to cancer treatment, Ben Ayed was spurred to greater action by seeing patients in distress. In 1987, with friends and co-thinkers, he created the Tunisian Association for the Fight against Cancer (ATLCC), and in 2000, the Association for the Promotion of Pain and Palliative Care.

In the hands of Ben Ayed, the ATLCC has grown into a humanitarian and scientific association with a public service brief, that also promotes teaching and prevention.

Thirty percent of cancers in Tunisia are linked to the environment and 40% to tobacco, especially cancers of the lungs, throat and bladder. The campaign against tobacco has become the top priority for the association. This ranges from efforts to convince farmers to replace tobacco cultivation with other crops, to lively teach-in sessions in partnership with the train company SNCFT on one of their busiest commuter lines. Indeed, 'smokeless' trains have become a renowned feature of World Anti-tobacco Day, attracting positive coverage on Tunisian press and television (although they revert to being 'smoking' trains the next day).

Ben Ayed is committed to change in a country where virtually half of men smoke. (A World Health Survey in 2003, showed that 49.5% of men over the age of 18 smoke, while only 2.4% of women over the age of 18 do so.) He said: "I admire the Canadians and Irish for their willingness to confront the tobacco lobby and take effective action. In Tunisia we have adequate legislation, but nobody takes any notice. In a recent study we found that 95% of people are well aware of the risks. Our aim is not just to inform but to change behaviours."

He believes in the value of engaging children at school about the risks during special national and regional anti-tobacco days. When children go home they take with them the knowledge and arguments they have heard – a powerful means to debunk myths with parents and family.

Education, training and information are the bedrock of the ATLCC prevention strategy. Special programmes, such as palpation techniques for breast examinations, are aimed at the general practitioner (GP), who is seen as the first line of defence. Ben Ayed believes that the GP must also be an educator and a communicator.

National training days, conferences and seminars are other useful ways to reach specialists. A two-day international seminar was organised in Tunisia by Ben Ayed and Franco Cavalli from Bellinzona, Switzerland, with the European School of Oncology in December 2005.

The ATLCC is often at its most creative

when raising money. It raised funds to buy the first mammography machine for the Cancer Institute and teamed up with a chemical company to buy another for Gabès hospital in the south.

The success of the association shamed the authorities into action. Treatment centres opened in Sousse and in Sfax. The Government also released land to the association to build Eddar hospice. It was built with hard work and determination – a dinar here and a lorry-load of bricks there – with Ben Ayed as motivator, campaigner and executive. He asked students at the school of architecture to lend a hand with the design. He begged students elsewhere to sell postcards for a year to furnish it.

Since its launch in 1993, the hospice has lodged more than 1,000 cancer patients, most of whom needed somewhere to stay during treatment in Tunis. Thousands of other patients have received financial help. Ben Ayed says that the tremendous wave of solidarity around building the hospice grew stronger after it opened. "Scores of volunteers are involved day in, day out, in a loose support network. Some prepare the food, others just give moral support."

Now Ben Ayed has set his sight on building, with the help of the Ligue française contre le cancer and the UICC, an information centre to be used by the public and the media, as well as by students and health professionals.

Leading oncologists do not often vacate their labs to negotiate deals with outside organisations. One of the most imaginative was with the national train company. Backed by the cancer institute, the association agreed to screen the rail company's female staff for cervical cancer, in exchange for SNCFT agreeing to transport cancer patients to and from treatment centres free of charge.

Another idea was to recycle printer cartridges, which raised awareness about environmental issues and paid for a mammography machine.

Ben Ayed says: "With limited resources, the only option open was to innovate and develop activities commensurate with what is achievable. In Tunisia everything is a priority, but this should not be an excuse for doing nothing. We should be able to take care of our needs and better manage our expenditure."

Ben Ayed with Henda Raïs, the first doctor in Tunisia to be trained as a specialist for pain and palliative care in cancer

The association has also focused on developing palliative care, becoming the local chapter of the International Association for the Study of Pain.

It has found time to address ethical issues, bringing together a philosopher, a jurist, a nurse and a sociologist to discuss clinical research and trials. Ben Ayed brought in his own expertise as a member of the French and Francophone Society of Medical Ethics at University Paris V.

He concludes that value judgements are not the same everywhere. "Ethics concerns personal behaviour but it is also a reflection of society. However, we found in the end no difference between different religions in their stand on ethical questions."

Ben Ayed is renowned for saying little and saying it quietly. He abhors loud plaudits. He grapples with philosophical concepts and aspects of humanity beyond what can be recorded on charts and medical records. Without raising his voice, he sums up his quest: "I want Tunisians not to be afraid of cancer anymore."

Not (just) another declaration

Peter McIntyre

The World Cancer Declaration, issued in July, aims to mobilise efforts behind a limited number of aims that will make a big difference and can be quickly achieved.

The World Cancer Declaration adopted at the UICC Congress in Washington this summer aims to be different from other closing statements – longer on action than in words.

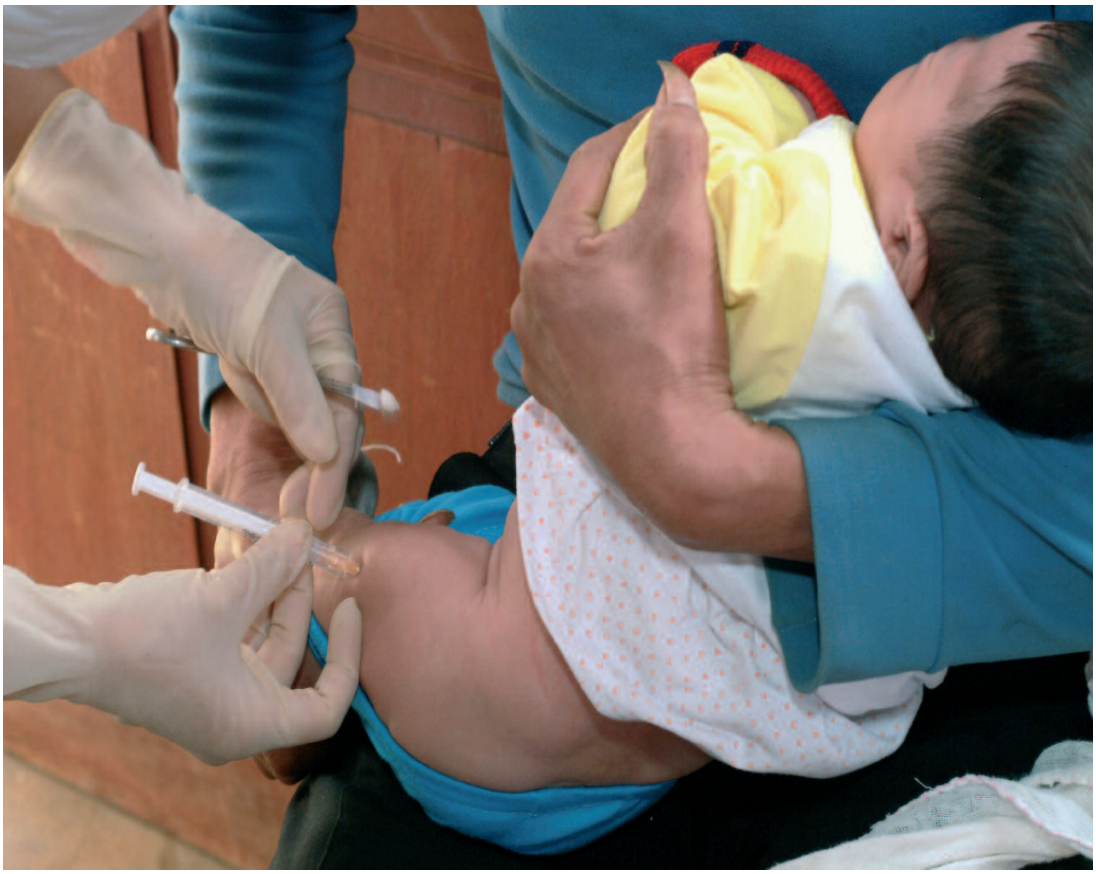
Most conferences end with a declaration or statement, and most vanish into the ether. Nobody has yet been cured of cancer, or even of the common cold, by rhetoric. Without hard slog to turn the rhetoric into action, conventions and declarations are soon forgotten.

On the other hand, declarations can play a valuable role in setting agendas, focusing attention on the main issues, and bringing people together to work in the same direction.

The cancer world has had its share of big statements in recent years. In 2000, the World Summit against Cancer in the New Millennium adopted the Charter of Paris. This adopted a rights agenda, and focused on early detection, translational research, clinical guidelines, evidence-based medicine, quality of life and patient advocacy. Most people remember another outcome of the summit better than the ten articles and preamble of the Charter, since this was the meeting that established 4 February each year as 'World Cancer Day'.

In May 2003, the World Health Assembly (WHA), the global 'Parliament' of the World Health Organization, opened the WHO Framework Convention on Tobacco Control for signature. The FCTC came into force in February 2005 and has become one of the most widely embraced treaties in the history of the United Nations. This was seen as a declaration of war on the harmful effects of tobacco, and has strengthened international campaigns against the tobacco industry. However, the 38 Articles and more than 9,000 words are not especially memorable. And many governments have proved readier to sign it than to take action afterwards.

In May 2005, the WHA, "alarmed by the rising trends of cancer risk-factors, the number of new cancer cases, and cancer morbidity and mortality worldwide, in particular in developing countries," passed a landmark resolution on



PHILIPPE BLANC / ANGALIA-PHOTO

Anti-cancer vaccination. Adding Hepatitis B to child immunisation programmes like this one at the Hai Linh Commune Health Centre, in Vietnam, will have a significant impact on the incidence of liver cancer – one of the most prevalent cancers in some areas of the world

cancer prevention and control that set the agenda for comprehensive national cancer control plans in each country. For the first time the WHO declared cancer to be a priority issue for all governments. This has given a tremendous boost to global efforts on cancer, but the comprehensive nature of the resolution and the plodding UN language, means that it is hardly a call to arms.

The World Cancer Declaration adopted at the UICC World Cancer Congress in Washington July 2006 sets out to fill the gap. It does not set a new agenda, but attempts to identify strategic and urgent steps that cancer organisations and campaigners can address in the short term. This is unashamedly an advocacy declaration, designed to give a much higher profile to cancer and to put it on the political and public agenda.

At under 1,000 words, it is less than half the length of the Charter of Paris, and the nine key calls to action are admirably brief. It was the result of widespread consultation and has the support of high-profile global intergovernmental agencies. However, the Declaration was essentially produced by NGOs, so it has natural allies to work with it in every country.

The Declaration has a short shelf-life, since progress will be monitored and reported to each World Congress, after which it will be redrafted. It must therefore show results by the next UICC Congress in Geneva in August 2008.

Relative simplicity was not easy to achieve. Responsibility for the early drafts rested with the hosts for the Washington Congress, the American Cancer Society (ACS). Ten months in advance of the Congress, the ACS and UICC trawled a list of 250 experts worldwide for ideas about what it should contain. Unsurprisingly, the first draft ran to 20 pages.

This draft went back to the experts and global bodies (WHO, IARC etc) for comment. The

WHO

The next generation. Can we stop the sort of smoking epidemic that ravaged Europe and America a generation ago from being replicated in developing countries?

second draft was even longer. Then began the process of simplifying and clarifying – it took six or seven drafts to achieve the short version. At the Congress itself, participants were given three days to comment on the draft, and suggestions were made at a 'World Leader Summit' – although the Declaration hardly changed at this late stage.

Franco Cavalli, President of the UICC, says that brevity and clarity were key aims, as it is important that the Declaration is backed with action. "Of course, the World Cancer Declaration is based on the Charter of Paris, but the idea was to have something which could have much more immediate results, to pick topics that seem to be the most important and urgent and to summarise them very briefly. The Charter of Paris is a declamatory declaration without immediate consequences; here we are trying to have consequences.

"It is not enough to have governments signing declarations, you need interventions from civil society to push governments to realise what they have written. Here the driving forces were NGOs. We are trying to follow the example of the AIDS NGOs, which have been able to put the topic of AIDS on the political and media agenda, which, alas, has not yet been the case for cancer."

Cavalli admits that he was initially sceptical, but is increasingly enthusiastic about the Declaration's power to mobilise. He was at the Chinese Congress on Cancer in October, organised by the two major Chinese associations. They further reduced the World Cancer Declaration to six points, set priorities for combating cancer in

The Declaration was essentially produced by NGOs, so it has natural allies in every country

"I have the impression that this is starting to create a little avalanche which is increasing in speed"

China, and adopted it as "the Tianjin Declaration". At a meeting in Bangkok in early November – Empowering Cancer Prevention in the Asia Pacific – the Declaration was also a topic for debate in many of the sessions.

"What I am hearing is much more positive than what I expected. I have the impression that this is starting to create a little avalanche which is increasing speed. The fact that such a declaration has been launched is a sign of the momentum which is being created currently about the emerging problem of cancer in the developing world. There was an editorial by Peter Boyle in the *Lancet* and I published an editorial in the last issue of *Nature Clinical Practice Oncology*. This is part of a movement which is just starting to roll."

The Declaration says that it "requires partnerships between governments, private sector, non-governmental organisations, and international organisations".

Cavalli cites the PACT global partnership that brings together governmental and non-governmental entities involved in cancer control, as a good example. "There are different types of partnership. I think that the private sector is to be understood mainly in the sense that NGOs and private organisations should be also very much involved. As regards the private sector in the narrower sense, meaning private hospitals and structures, this is so different from country to country, it is in my opinion very difficult to have a general statement. If you set up a cancer control plan you have to include NGOs and the private sector, but the responsibility of course lies with the government. That is quite clear."

The Declaration has been translated into several languages and is now being distributed worldwide amongst UICC members. The UICC is preparing an action plan based on the Declaration, and is talking to WHO about monitoring progress. "We want to monitor where we will be in 2008 so we can judge progress," says Cavalli. "We will see whether there will be 10 or 15 countries more with a cancer control plan than in the past."

The full text of the World Cancer Declaration can be downloaded at http://www.uicc.org/

WORLD CANCER DECLARATION – SUMMARY

The World Cancer Declaration predicts that by 2020 there will be 16 million new cancer cases and 10 million cancer deaths each year, with 70% of the deaths in developing countries. It says that cancer can be eliminated as a major threat, but only if cancer control is made a priority for the decade.

PRIORITIES:

- **Investing in health:** with compelling messages to win the argument for countries to invest in cancer prevention and control
- **Cancer control planning:** increasing the number of countries that have national cancer control plans with budgets
- **Cancer surveillance:** increasing the number of countries with adequately funded cancer surveillance systems
- **Tobacco control:** increasing the number of countries implementing successful initiatives connected with the WHO Framework Convention on Tobacco Control
- **Vaccines:** developing an international plan for HPV vaccination in low- and middle-income countries, and integrating Hepatitis B into infant vaccination programmes
- **Early detection/treatment:** adopting evidence-based guidelines for early detection and treatment tailored to socioeconomic, cultural and resource settings
- **Palliative care:** increasing the number of countries that make pain relief and palliative care an essential service in cancer treatment and home-based care
- **Mobilising individuals:** empowering those affected by cancer to participate in cancer control efforts
- **Supporting steps:** implementing a process to monitor actions, report on progress and identify organisational roles

Closing the survival gap

Anna Wagstaff

EU countries from Central and Eastern Europe are trying to close the gap with Western Europe in cancer prevalence and survival rates. In Ljubljana, politicians, experts and patients came together to debate cancer plans, political will, funding and ways to stop skilled staff leaving home.

It had been a year since the signing of the Warsaw Declaration on cancer services in Central and Eastern Europe – long enough perhaps for politicians to have forgotten their undertakings and moved on to other issues.

Instead, a critical mass of MPs, MEPs and health administrators gathered in the Slovenian capital, Ljubljana, in November 2006 to renew their commitment to closing the gap between cancer outcomes in the east and west of Europe, and to discuss ways of making it happen.

This was a working conference, organised by the European Cancer Patient Coalition, at which politicians, cancer experts and patients groups from all over Europe dedicated time to working out how to ensure that the aims of the Warsaw Declaration are fulfilled.

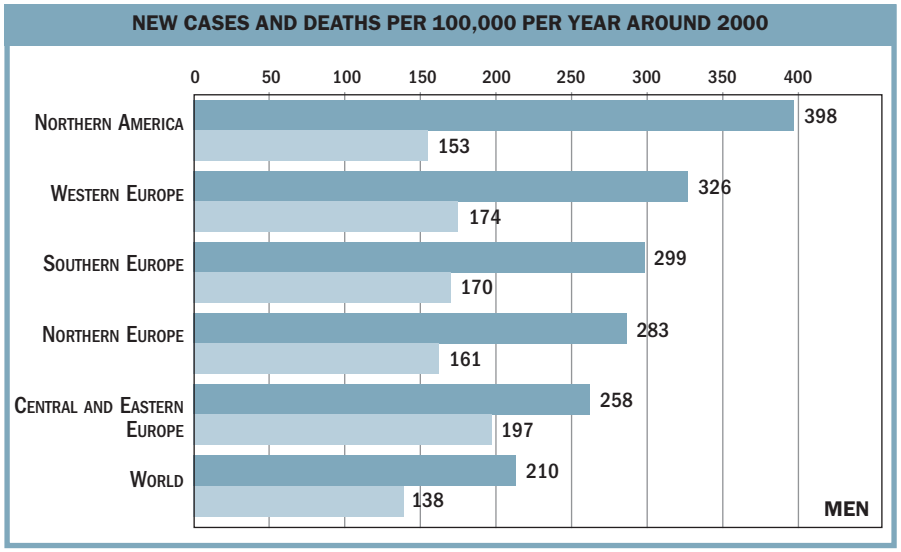
Given equal services, people in Central and Eastern European (CEE) countries should be at lower risk of dying of cancer, because these countries have the fewest diagnosed cases in the whole of Europe. However, women in CEE countries are only slightly less likely to die of cancer than their sisters in Western and Northern Europe, while CEE men are much more likely to die than their counterparts.

In the period 1983–1994 the survival statistics in some CEE countries improved, but more slowly than the average for the rest of Europe. In some CEE countries, survival rates actually fell. So, the gap between east and west is growing rather than narrowing.

"Do our governments know about these figures?" asked a representative from the Institute of Patients Rights in Poland. "Where can we find copies of these statistics?" asked another delegate (answer: www.eurocare.it). Irena Belohorská, medical oncologist and Slovakian MEP, had heard the statistics for the first time at the October conference of the European Society for Medical Oncology. Two days before travelling to Ljubljana, she presented them to her health minister. "He was shocked," she said.

The conference heard presentations about the two most comprehensive programmes implemented in Europe to date. The French and UK Cancer Plans both tackle cancer from prevention and early detection to training, guidelines, organisation of care and rehabilitation. The French plan also addresses social issues such as rights at work. Many delegates cited these contributions as giving helpful information to take home.

Ariana Znaor from the Croatian National Institute of Public Health valued the precision of the UK experience. "What I found useful was the setting of very specific targets," she said. She was also impressed by the patient-orientation of the



Unacceptable. Men in Central and Eastern Europe have a lower incidence of cancer than men in other parts of Europe, but mortality rates are significantly higher *Source: Globocan 2002, IARC*

French plan – "Cancer care in many places ends after the patient is sent home from hospital."

Mihály Kökény, chair of the Health Committee in the Hungarian parliament, was similarly inspired. "Many of our currently good and valid national cancer plans and programmes should be much more citizen- and patient-centred. We need to support patient groups, and involve them. Cancer is an important issue but it cannot just be left to the medical people."

A PLACE ON THE AGENDA

In many CEE countries, cancer remains taboo, denied a profile in public life and the media, with no chance of becoming a political priority. Both Mike Richards, architect of the UK Cancer Plan, and Brigitte Guillemette from the French National Cancer Institute, stressed that advances had only been possible with top-level, sustained political support. The Ljubljana gathering was itself in part the result of political backing from former Slovenian President, Alojz Peterle, the founding spirit and vice-chair of MEPs Against Cancer.

Countries struggle to break free of a negative mind-set. Simone Ene, who works with the Association of Cancer Patients in Romania, says that people and politicians "are blind to the issue of cancer. They treat cancer as a fatal disease not a chronic one."

But there is evidence that things are beginning to change. Evgenia Adarska, president of the cancer patients group, APOZ, reported a political and media storm in Bulgaria, when a member of the parliamentary health committee said: "It is immoral to ask for more money for oncological treatment because cancer patients are already dead." The MP was disciplined – and Bulgaria's cancer patients now stand to gain from the 30% increase in the health budget they had been fighting for.

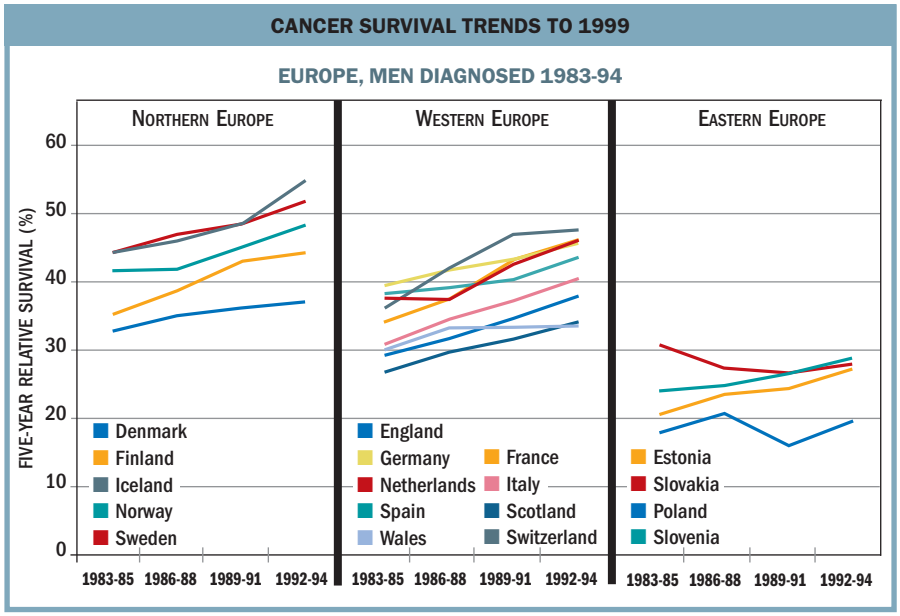
In Hungary too, Kökény says that people have started talking publicly about cancer – as part of a general climate of greater openness. "Developing cancer care was not an area that local politicians and the government felt should be a priority. It was swept under the carpet. Now everyone has to face the statistics."

RESOURCES AND STAFF

However, there remains a problem with funding. Znaor, from Croatia, points out that CEE countries missed out on support from Europe Against Cancer because it ended before they joined. "Organised screening programmes are major undertakings that don't give quick results, and cost a lot of money."

Transformation from the old socialist systems has taken its toll, while countries involved in the fighting that accompanied the break-up of Yugoslavia are still trying to rebuild their infrastructure.

Fatmire Mulhaxha-Kollçaku chairs the Committee on Health, Labour and Social Reform in the Kosovan parliament. As part of Yugoslavia, Kosovo was progressively starved of resources, she said. The unresolved separation from Serbia left Kosovo without any oncology centre or even a radiotherapy facility. These are having to be constructed from scratch, by an administration that is struggling even to get its telephone system functioning properly. Infectious diseases account for much of the Kosovo health budget, as many villages still lack sources of clean water. Her entire



A growing gap. Survival rates are improving faster in Northern and Western countries than in Eastern Europe, which means the survival differences are increasing *Source: Coleman et al, 2003*

budget for chronic diseases, including cancer, heart disease and diabetes is 3 million euros, for a population of 2 million people.

Even peaceful change has brought problems. In Slovakia, transformation brought decentralisation of the health service. Belohorská says that one result is that poorer regions get a poorer quality service, while a shortage of nurses has led to the closure of many beds. "The plan is not the problem. There is not the money."

Belohorská sees staff shortages as the single greatest threat to cancer care and cancer screening, as specialists and nurses exercise their EU labour mobility rights to work in better paid parts of Europe. Patients, she points out, are not so mobile and are left high and dry. Ene from Romania agrees. "You have to give [doctors and staff] a reason to stay – increase their salary and improve their working conditions. You can't just give them the opportunity to run off and leave the patients to die."

Can the EU add value?

Belohorská asserts that a failure to allow the EU a greater role in health policy in the member states amounts to "punishing the people" and says that "without healthcare it is not the Europe of the people."

However, the Ljubljana conference explored some of the ways in which the EU can help to move things forward. The 10 EU countries that joined in 2004 can choose six priority areas for structural funds, which could be put towards revamping and reorganising health services, screening programmes or staff training, and could free up money for increased salaries to keep doctors and nurses in the country. Hildrun Sundseth, conference organiser and head of the Brussels office of the European Cancer Patient Coalition, appealed to MEPs, MPs and patient groups alike to argue the case for investing in cancer. Cancer plans, she said, were also on the agenda for the next meeting of MEPs Against Cancer.

An acute awareness of the benefits of national, quality-assured screening programmes, including one for colorectal cancer, was evident across all the countries.

Joaquim Gouveia, Portugal's first National Coordinator for Oncology Diseases, emphasised the importance of creating a "common language of indicators and effectiveness studies", and said that benchmarking could be crucial to bringing cancer control in all countries up to the level of the best.

Kökény supports the need for standardised data, even down to individual hospital level on waiting times, caseloads, complication rates and so on. He mentions three areas where he would like the EU to take a lead. On smoking – Hungary has by far the highest incidence of male lung cancer in Europe – Kökény would like to see a binding directive. On drug prices, he wants an EU discussion about how to make new cancer drugs more accessible. On research, he believes Europe should be far more ambitious, and cites the opportunities presented by ideological opposition to genetic research in the USA.

This was an important milestone in the process of getting cancer onto the public and political agenda

Jan Potočnik, EU Commissioner for Research, welcomed a discussion on the merits of research, and assured the conference that cancer has been steadily moving up the agenda for allocation of funds from EU framework programmes.

Two years ago, the EU Clinical Trials Directive caused widespread dismay as it failed to take account of the need to conduct independent, academic clinical research. Potočnik made it clear that he does recognise the vital role of such work. He said that the forthcoming Research Framework Programme would link research, prevention, diagnosis and treatment, emphasise translational research, back the identification of best clinical practices and optimise the use of cancer registries for cancer research.

He acknowledged concerns over the failure to agree a Europe-wide validation system for continuing medical education (CME) to keep physicians up to date in a rapidly changing field.

Top priority

The Ljubljana meeting was another important milestone in the long process of getting cancer onto the public and political agenda. The journey has included the emergence of patient advocates, national cancer plans, the Europe Against Cancer programme (1985–2000), the development of a European network of cancer registries, the establishment of the European Cancer Patient Coalition (2004), the first meeting of EU health ministers on cancer (Paris, 2005), and the launch of MEPs Against Cancer (2005). Ljubljana brought many elements that reflect this progress together in the same room.

Slovenia's secretary of state for health, Dorjan Marušič, said that there was clearly a strong will "to continue on this track, to share ideas, to find solutions – not just at the level of experts and citizens but also at a political level." During a political roundtable discussion, MEPs, MPs, experts and patients decided to meet again in 2007 to continue the dialogue.

For Marušič, this is part of the build-up to the Slovenian EU Presidency in 2008, which they intend to use to give the fight against cancer a top priority. This will offer an unprecedented chance for patients, experts and politicians to push the issue up the agendas in their own countries.

It could also give a boost to patient power across Europe. Alojz Peterle, a prime mover behind the conference, has himself been diagnosed with prostate cancer and is standing for the Slovenian Presidency. Were he to win, the EU would, in 2008, have a cancer patient advocate at its head for the first time.

THE WARSAW DECLARATION

The Warsaw Declaration was launched at the second summit of cancer patient and advocacy groups in Central and Eastern Europe in November 2005, and called for urgent action to close the gap between CEE countries and the rest of Europe in cancer prevalence and survival rates.

1. Develop national cancer plans, setting priorities and allocating resources, for improving cancer control and research in all CEE countries and assure patients' groups monitoring over the implementation of these plans.
2. Invest in cancer prevention by promoting awareness, information and education campaigns about the risk factors of cancer, building on the ***European Code against Cancer***.
3. Invest in national screening programmes as recommended by the European Union; and implement high-quality EU standards to support early diagnosis.
4. Make high-quality up-to-date treatment, rehabilitation and care attainable for all cancer patients throughout Europe.
5. Encourage and ensure patient participation in all decisions on health policy and health care affecting cancer.
6. Advance cancer control as a priority for action where necessary to qualify for grants from the EU Structural Funds.
7. Oppose discrimination because of age, race, gender, domicile and economic status in respect of the latest cancer treatment.
8. Encourage and adopt national Charters of Patients' Rights according to European guidelines.

The full text plus a list of signatories can be found at www.cancerworld.org/ecpc

Gene expression profiling for individualised breast cancer chemotherapy: success or not?

John Ioannidis

Results of a recent study indicate that gene expression profiling seems to improve prediction of chemotherapy effect in breast cancer, but methodological caveats remain worrisome.

A study by Paik et al. (see opposite) has shown that a well-characterised recurrence score (RS) using information on the expression of 21 genes can successfully separate women who benefit from breast cancer chemotherapy from those who do not. Their study has several strengths: the RS has been developed with careful attention to both laboratory and statistical procedures and has been standardised to become commercially available, RS has already been found to predict recurrence and survival in a validation dataset (NSABP B-14),[1] and a meticulous training phase was carried out using three independent databases to maximise generalisation. Moreover, the treatment–RS interaction is demonstrated in 651 node-negative, oestrogen-receptor-positive women, a sample size much larger than used for most previous research on gene expression profiles.[2]

The interaction term between treatment and RS identified by Paik et al. has borderline statistical significance (P=0.038). Interestingly, even though the study population is derived from a randomised trial (NSABP B-20), the distribution of RS levels differs significantly between the tamoxifen and the tamoxifen plus chemotherapy arms (P=0.036). This result illustrates that biases and chance alone may yield similar P values to those found for the interaction term; however, an interaction is not necessarily required for a predictive score to be useful in therapeutic decisions. In the low-risk group, absolute risk is so low that chemotherapy is not recommended in any case.

The question is whether RS provides treatment guidance in addition to that available using routine information (e.g. age, tumour grade and receptor levels). RS correlates with and might be more informative than these classic predictors; however, even age, while clearly seen to have an interaction with the treatment effect in the full NSABP B-20 database, did not reach nominal significance in the 651 patients analysed in this study, owing to limited power. We need very large studies to discern the exact incremental benefit of RS interactions over classic predictors. Such predictors, which are routinely available, should be included in prognostic models.

The greatest concern regarding Paik et al.'s study is that tamoxifen-treated patients from the NSABP B-20 study were used in the original development of the RS, and data from these patients were important in the selection of the 21-gene signature[1]. RS is thus expected to (and does) differentiate the risk within the tamoxifen arm, since it has been trained purposely on these data. Conversely, RS does not appropriately differentiate recurrence risk in the NSABP B-20 chemotherapy arm. This contrast of good predictive performance in the tamoxifen arm and poor performance in the chemotherapy arm is what causes the significant treat-

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ment–RS interaction effect. Given that the tamoxifen arm was a training dataset, the correct interpretation of the data is not necessarily that RS is a superb predictor of treatment response. An alternative interpretation is that RS, while previously validated in the independent NSABP B-14 dataset,[2] now fails to be validated in the independent data of the chemotherapy arm of NSABP B-20.

As gene expression profiling moves from exploratory research into clinical practice, rigorous testing with fully independent validations should continue.[3] Useful molecular signatures need to be trained and tested on several thousands of patients.[4] The validation work to date is retrospective and thus provides only preliminary evidence. The TAILORx trial, a large prospective trial of 8,000 patients, will try to validate this 21-gene signature in the clinical setting. Similarly, the MINDACT trial will try to prospectively validate a different 70-gene prognostic signature. As we move into large-scale evidence, making sense of gene expression profiling remains a fascinating challenge.

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Synopsis

S Paik, G Tang, S Shak, et al. (2006) **Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer.** *J Clin Oncol 24:3726–3734*

Background. A 21-gene recurrence score (RS) assay has been developed and validated to quantify the probability of distant recurrence in women with node-negative, oestrogen-receptor-positive breast cancer.

Objective. To determine whether the RS can also predict the magnitude of chemotherapy benefit.

Design and intervention. Tumour tissue samples were obtained from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-20 trial, which investigated the value of adding chemotherapy (methotrexate and fluorouracil with or without cyclophosphamide) to 5 years of tamoxifen therapy in 2,363 patients with node-negative, oestrogen-receptor-positive breast cancer. Patients were enrolled between 17 October 1988 and 5 March 1993. Gene expression was measured using the Oncotype DX assay (Genomic Health Inc., Redwood City, CA). Each RS was determined by measuring the expression of 16 cancer-related genes and 5 reference genes, and was calculated on a scale of 0–100. Prespecified cutoff points for low-risk, intermediate-risk and high-risk disease were RS<18, RS in the range 18–30, and RS ≥ 31, respectively.

Outcome measures. The primary endpoint was freedom from distant recurrence. Cox proportional hazards models were used to study the interaction between chemotherapy treatment and RS as a continuous variable. Analysis was also performed using the predefined RS risk categories.

Results. Gene expression results were successfully obtained for 227 patients treated with tamoxifen alone and 424 patients treated with tamoxifen plus chemotherapy. Patients did not benefit equally from chemotherapy; those with a high risk of recurrence had a greater magnitude of benefit from chemotherapy than those with an intermediate or low risk of recurrence. Adding chemotherapy to tamoxifen improved the 10-year Kaplan–Meier estimate for freedom from distant recurrence from 60% to 88% in the high-risk group. The high-risk category benefited from chemotherapy, with a large reduction in distant recurrence at 10 years (relative risk [RR] 0.26, 95% CI 0.13–0.53; decrease in absolute risk 27.6%). This benefit was less clear for patients in the intermediate-risk group (RR 0.61, 95% CI 0.24–1.59; increase in absolute risk 1.8%), but a clinically important benefit from chemotherapy could not be excluded. No reduction in distant recurrence at 10 years was demonstrated for patients in the low-risk category (RR 1.31, 95% CI 0.46–3.78; increase in absolute risk 1.1%). In a multivariate analysis, the interaction between chemotherapy treatment and RS was significant (P=0.038); however, no clear cutoff point for RS could be defined.

Conclusion. The RS can predict the magnitude of benefit from chemotherapy for patients with node-negative, oestrogen-receptor-positive breast cancer, as well as the likelihood of recurrence of breast cancer, and could be used to select patients who would respond well to chemotherapy.

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

Poor correlation between physician and patient assessment of quality of life in palliative care

Eduardo Bruera

Wide variations found between quality of life assessments made by patients and by physicians indicate that patient symptom expression is a complex multidimensional construct.

In a recent study (see opposite), Petersen et al. observed a poor level of agreement between patient and physician assessments of patients' health-related quality of life (HRQOL) on first contact, with no significant improvement during follow-up encounters. My research group made a similar observation in 49 patients admitted to an acute palliative care unit,[1] with a tendency for physicians to underrate most symptoms, particularly sedation, shortness of breath, and pain. Other authors have observed both underrating and overrating by health-care professionals.[2] These findings emphasise the need for routine patient-based symptom assessment in the clinical setting. Unfortunately, except for pain evaluation, such assessments are infrequent in clinical practice, even within palliative care centres. Even for pain evaluations, the accuracy of these assessments when conducted within regular clinical care has been questioned.[3]

Why does this discrepancy occur? It is possible that physicians do not appropriately assess the intensity of some symptoms, because of limited time, or insufficient focus on emotional distress when debilitating physical symptoms are present. Another possible interpretation is that palliative care physicians make consistent errors in symptom assessment. An approach that considers the patient's numerical report regarding their symptoms as the 'gold standard' would reach this conclusion. The patient's self-rating of symptom intensity needs to be interpreted as a multidimensional construct, however.[4-5] It is not possible to measure the actual production of nociceptive input from a painful bone metastasis, the production of afferent dyspnoea by 'J' receptors in the lung or respiratory muscles, or the afferent nausea stimulus emerging from the gastric wall to produce numerical representations of the primary pathophysiological mechanisms. The perception of these stimuli within the somatosensory cortex also cannot be measured. A number of inhibitory and facilitating pathways are capable of altering the intensity of symptom perception. Finally, the numerical rating reflects the individual's expression of symptom perception, which may be significantly affected by their belief about the nature of the symptoms, their understanding of the assessment tool, and cultural and social factors.

The impact of this numerical rating on the treatment of the patient's symptoms has to be taken in context. For example, a pain intensity score of 8/10 in a patient whose pain had been consistently scored at 2 or 3, and who has experienced considerable tumour growth, is likely to overwhelmingly reflect increased nociceptive input and require specific analgesic therapy. On the other hand, a pain intensity score of 8/10 in a patient who has been consistently expressing similar intensity for several months and who has a history of heavy chemical dependence is much less likely to reflect nociceptive input and will, therefore, require less analgesia and more psy-

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chosocial interventions. Symptoms such as fatigue, nausea, or dyspnoea are subject to similar levels of variability.

Patients and palliative care physicians could be interpreted as contributing complementary rather than opposing information from different perspectives. Using generalisability theory, it might be possible to reach a better understanding of the multidimensional construct included in each of the different symptoms reported by patients.[5] Future research should focus on the influence of mood, delirium, chemical coping, and so on.[6] In addition, qualitative studies should be conducted to better characterise how palliative care physicians make decisions when noticeable differences are observed between their interpretation of a symptom and that symptom as reported by the patient.

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Synopsis

MA Petersen, H Larsen, L Pedersen, et al. (2006) **Assessing health-related quality of life in palliative care: comparing patient and physician assessments**. *Eur J Cancer 42:1159–1166*

Background. Assessment of the efficacy of palliative care measures is subject to a number of biases, linked to difficulty in patient recruitment and the severe attrition that must be expected because of deterioration in patient condition or early death. Although patients' assessment of their own quality of life must be considered the 'gold standard', the use of 'proxy' assessments (e.g. from nurses, clinicians or family) could improve the range and applicability of studies in palliative care. It is important for accuracy, however, that these proxy assessments concur with patients' own ratings.

Objective. To determine the reliability of physician assessments of patients' health-related quality of life (HRQOL) in palliative care compared with patient assessments.

Design. This was a longitudinal study in adult palliative care patients with breast, colorectal, gynaecological, head and neck, lung or other cancers, seen at a single centre and being managed as inpatients, outpatients, or with home care.

Intervention. Between June 1998 and August 2003, patients and physicians completed questionnaires including items from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-C30, at their first contact, and then weekly for 13 weeks or for as long as the patients wished or were able to continue.

Outcome measure. The outcome measure for this study was the degree of agreement between patients' and physicians' assessment of HRQOL at first contact and for the following 13 weeks of care.

Results. At the first assessment, 115 patients met the inclusion criteria. A high number of patients were not able to complete 13 full weeks of the study (only around 25% of patients were still alive 13 weeks after referral); therefore, the authors focused primarily on the initial questionnaire and used data from the further time points (weeks 1–13) to verify their findings. Agreement between patients and physicians was poor overall. Patient and physician assessments were significantly different for all HRQOL domains assessed ($P<0.01$ for all). Generally, physicians judged that patients had fewer symptoms and better functioning than did their patients, the exceptions being physical and social functioning. The smallest absolute differences (indicating better reliability) between physician and patient assessments were seen for physical functioning, nausea/vomiting and constipation, and the largest absolute differences were seen for insomnia and two psychosocial scales: emotional and social functioning. The overall agreement between patient and clinician for the period of time following admission was no better than at the admission consultation.

Conclusion. The authors conclude that, despite their experience, physicians working in palliative care have very different perceptions of patients' HRQOL than do their patients themselves. The use of physician assessments in palliative care studies may bias findings and should not be considered a viable alternative to patient self-assessment.

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NEWSROUND

Selected press reports compiled by the ESO Cancer Media Centre

No advantage to giving advanced lung cancer patients more than three courses of chemotherapy

→ British Journal of Cancer

A study has found that giving patients with advanced non-small-cell lung cancer (NSCLC) more than three courses of chemotherapy does not improve quality of life or survival. It is important that patients are not overtreated with drugs that offer no survival benefits and are associated with burdensome side-effects.

Despite improvements in cancer treatment, patients with NSCLC, the most common form of lung cancer, often have a poor prognosis. The latest research looked at the optimal duration of palliative chemotherapy for patients with NSCLC.

Two hundred and ninety-seven patients with advanced NSCLC (stage IIIB or IV) were randomised to receive either three or six courses of the latest platinum-based chemotherapy (carboplatin and vinorelbine). Eighty-eight percent of the patients completed an EORTC Quality of Life Questionnaire. The researchers also analysed overall survival data.

The study found that there were no significant differences between the groups in quality of life, pain or fatigue up to 26 weeks. Two-year survival rates were 9% in the arm that received three chemotherapy treatments compared to 5% in the arm that received six rounds of chemotherapy, but the difference did not reach statistical significance. The study concluded overall that palliative chemotherapy with carboplatin and vinorelbine beyond three courses gave no survival or consistent quality of life benefits in advanced NSCLC.

■ Palliative chemotherapy beyond three courses conveys no survival or consistent quality-of-life benefits in advanced non-small-cell lung cancer. C von Plessen, B Bergman, O Andresen, et al. for the Norwegian Lung Cancer Study Group. *Br J Cancer* 23 October 2006, 95:966–973

More colorectal cancer patients should receive recommended surgery

→ JNCI

A recently published study has shown that only one-third of US American patients who underwent surgery for locally advanced adherent colorectal cancer received a multivisceral resection, a procedure proven to reduce local recurrence and improve survival compared to standard resection.

An assessment of 8,380 patients from the US Surveillance, Epidemiology and End Results (SEER) registry revealed that only 33.3% of patients who had surgery for locally advanced adherent colorectal cancer underwent multivisceral resection. The remaining patients only had their tumour removed.

Compared with standard resection, multivisceral resection was associated with improved overall survival for patients with colon and rectal cancer, with no associated increase in early mortality. Patients who underwent multivisceral resection had significantly greater five-year survival rates (35.1% vs 27.7%).

Several factors increased the likelihood of receiving multivisceral resection, including younger age at diagnosis and being female. There was also a significant variation in the likelihood of receiving the procedure based on the geographical region in which patients were treated.

■ Population-based assessment of the surgical management of locally advanced colorectal cancer. A Govindarajan, NG Coburn, A Kiss, et al. *J Natl Cancer Inst* 18 October 2006, 98:1474–1481

Postponing surgery reduces long-term side-effects for children with kidney cancer

→ European Journal of Cancer

Children given chemotherapy before surgery to treat the most common form of childhood kidney cancer, called Wilms' tumour, require less treatment and experience fewer long-term side-effects than if they undergo immediate surgery.

The Children's Cancer and Leukaemia Group (CCLG) undertook a ten-year trial involving 205 patients with newly diagnosed Wilms' tumours. The patients were randomly assigned to receive either immediate surgery or six weeks pre-operative chemotherapy and then surgery. Depending on the size of their tumours and how much they had grown, all children on the trial were given chemotherapy, radiotherapy or both after their surgery to destroy any remaining cancer cells.

Overall survival between the two groups

was the same, but the researchers found that giving six weeks pre-operative chemotherapy enabled easier removal of tumours. Also 20% fewer children needed radiotherapy or treatment with doxorubicin after their surgery, minimising their risk of long-term side-effects.

The author of the study, Christopher Mitchell from the Oxford Radcliffe Hospital, said, "Deciding what is the best way to treat Wilms' tumours has been under debate for many years and this study was the first time that the two treatment methods were compared in a randomised clinical trial.... We were able to benefit a group of patients who could benefit from a reduction in treatment without compromising their survival chances. For some children with advanced tumours, delaying their surgery reduced the size of their tumours enough to prevent them needing intensive treatment after surgery. This improvement in quality of life for patients is significant and we hope children diagnosed with Wilms' tumours in the future will benefit from our findings."

■ Immediate nephrectomy versus pre-operative in the management of non-metastatic Wilms' tumour; results of a randomised trial (UKW3) by the UK Children's Cancer Study Group. C Mitchell, K Pritchard-Jones, R Shannon, et al. *Eur J Cancer* October 2006, 42:2554–2562

Breast cancer care is improving across Europe

→ International Journal of Cancer

A new study has found that breast cancer survival rates in some European countries have improved since 1970.

The study, conducted by a group at the Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, analysed and estimated breast cancer trends in 10 European countries from 1970 to 2005. Interpreting breast cancer survival data can be difficult, as activity such as improved screening and earlier diagnosis can inflate both incidence and survival. The study therefore analysed survival trends in relation to mortality and incidence in order to give an accurate overview of breast cancer trends.

The study showed that, in most countries included in the analysis, survival from breast cancer had improved and this could be attributed to better care. Those countries included Sweden, the UK, France, Italy and Spain.

The study also found that differences in incidence rates seen across Europe in the 1970s continued into the 21st century, with the lowest incidence in Spain and Italy and the highest incidence in the Netherlands, Denmark, Finland, Sweden, and France. In Finland, the Netherlands and Denmark, there was an increase in breast cancer mortality and incidence, indicating an increased breast cancer risk, probably related to life-style factors.

In Estonia, the research indicated that there was inadequate care for breast cancer patients, as there was poor survival in the context of increasing incidence and mortality.

The figures overall look promising and point to improved treatment helping patients live longer in the wealthier European countries. However the poor results from Estonia suggest that the survival and treatment differences in European countries continue to exist.

■ Time trends of breast cancer survival in Europe in relation to incidence and mortality. M Sant, S Francisci, R Capocaccia, et al. *Int J Cancer* 15 November 2006, 119:2417–2422

Maintenance therapy with thalidomide shown to have a role in multiple myeloma

→ Blood

There is no known cure for multiple myeloma, a cancer of the plasma cells. Current treatments involving high-dose chemotherapy have increased the response rate but more effective approaches are needed to maintain the duration of response.

Results from a randomised trial of maintenance therapy with thalidomide and pamidronate carried out by a team of European researchers were recently published. The study showed thalidomide is an effective means of maintaining duration of response in patients with multiple myeloma.

The study involved 597 patients divided into three groups. The first group was treated with the drug pamidronate alone, the second group with pamidronate and thalidomide and the third group received no maintenance therapy.

The researchers showed that, four years after diagnosis, the group treated with pamidronate and thalidomide had an overall chance of survival of 87%. Patients in the pamidronate-alone arm had a 74% probability of survival compared with those not receiving therapy, at 77%. The three-year probability of the patients remaining relapse-free was 36% without maintenance therapy and 37% with pamidronate alone. The addition of thalidomide significantly improved these odds, to 52%.

Pamidronate has been used by doctors to protect against bone damage; however, the study found that the drug did not decrease the number of bone events, as anticipated, and there was no significant difference in the number of these events between the three treatment groups.

However, thalidomide remains a powerful drug and difficult for some patients to tolerate. The drug was originally dosed at 400 mg per day, but after 15 months, the median dose was decreased by half because of drug-related toxicity. Thalidomide was discontinued in 39% of the patients taking the drug due to side-effects such as numbness, tingling or pain in the hands and feet, fatigue and constipation. In contrast, only 4% of patients discontinued pamidronate.

Patients most likely to benefit from the addition of thalidomide to maintenance therapy were those whose responses to the original chemotherapy were not as successful, and those who did not have a chromosome 13 deletion – an abnormality found in about 15–20% of patients with multiple myeloma and one that is associated with a poorer prognosis.

■ Maintenance therapy with thalidomide improves survival in multiple myeloma patients. M Attal, J-L Harousseau, S Leyvraz, et al. *Blood* 15 November 2006, 108:3289–3294

Common antibiotic is a useful treatment for rare lymphoma of the eye

➜ JNCI

The common antibiotic doxycycline effectively treats a type of lymphoma associated with chlamydia infection, according to a recent study. Ocular adnexal lymphoma of the MALT-type (OAL) is an uncommon type of non-Hodgkin's lymphoma that affects tissues surrounding the eye. It is not normally fatal, but its symptoms can affect a patient's quality of life. Some research has suggested an association between OAL and *Chlamydia psittaci* (CP) infection.

A group led by Andrés Ferreri from the San Raffaele Scientific Institute in Milan, Italy, examined whether doxycycline was an effective treatment for OAL. They gave 27 OAL patients a three-week course of doxycycline therapy, regardless of whether they were positive or negative for CP. They assessed lymphoma response at 1, 3 and 6 months.

The authors found that doxycycline treatment caused lymphoma to regress in both CP-positive and CP-negative patients. Failure-free survival at two years in the patients treated with doxycycline was 66%, and 20 of the 27 patients (74%) were progression free. The responses observed in patients who tested negative to CP may suggest a need for development of more sensitive methods for detection, and investigation of the potential role of other doxycycline-sensitive bacteria.

According to the authors, doxycycline may be a useful therapy even in patients where other treatments have failed, and it is a valid alternative to chemotherapy and radiation without causing the same toxic side-effects.

In an accompanying editorial, Emanuel Zucca and Francesco Bertoni, of the Oncology Institute of Southern Switzerland, advised "While doxycycline appears to be an easy-to-implement therapeutic approach, we strongly encourage all physicians to enrol patients in clinical prospective trials to help answer these questions."

■ Bacteria-eradicating therapy with doxycycline in ocular adnexal malt lymphoma: a multicenter prospective trial. AJM Ferreri, M Ponzoni, M Guidoboni, et al. *J Natl Cancer Inst* 4 October 2006, 98:1375–1382

Chemotherapy cuts the chance of rectal tumours returning by half but does not affect overall survival

➜ New England Journal of Medicine

Giving a patient chemotherapy before or after an operation to remove their rectal cancer cuts the chance of the tumour returning in the rectum by half. Unfortunately, it doesn't increase the patient's overall survival – according to a recently published study.

A total of 1011 patients were enrolled in the study to see whether giving rectal cancer patients radiotherapy before or after their operation affected their survival. The researchers also evaluated the benefits of adding chemotherapy to radiotherapy before or after the operation.

The radiotherapy was given to patients over a period of five weeks. The chemotherapy consisted of fluorouracil plus leucovorin daily for five days. There was no significant difference in overall survival between the groups that received chemotherapy preoperatively (P=0.84) and those that received it postoperatively (P=0.12). The combined five-year overall survival rate for all four groups was 65.2%. The five-year cumulative incidence rates for local recurrences were 8.7%, 9.6%, and 7.6% in the groups that received chemotherapy preoperatively, postoperatively, or both, respectively, and 17.1% in the group that did not receive chemotherapy (P=0.002). The rate of adherence to preoperative chemotherapy was 82.0%, and to postoperative chemotherapy was 42.9%.

Chemotherapy, regardless of whether it was given before or after surgery, did benefit the patient because it reduced the chance of the tumour coming back by half. However, fluorouracil-based chemotherapy administered either pre- or postoperatively had no impact on survival.

■ Chemotherapy with preoperative radiotherapy in rectal cancer. J-F Bosset, L Collette, G Calais, et al. for EORTC Radiotherapy Group Trial 22921. *New Engl J Med* 14 September 2006, 355:1114–1123

New cancer drugs approved for Europe

➜ European Medicines Agency

The European Commission has granted marketing authorisation approval for a number of novel cancer medicines. Novartis was awarded approval for Exjade (deferasirox), indicated for the treatment of chronic iron overload due to frequent blood transfusions in patients with beta thalassaemia major, aged six years or over. The agent can also be used in the treatment of chronic iron overload in patients with other anaemias where defoxamine therapy is contra-indicated. Topo Target's Savene (dexrazoxane) is now approved for use in the treatment of anthracycline extravasation. Merck Sharp and Dohme was given approval to market the vaccine Gardasil/Silgard to prevent high-grade cervical dysplasia, cervical carcinoma, high-grade vulvar dysplastic lesions, and external genital warts causally related to human papillomavirus types 6, 11, 16 and 18.

EMEA's Committee for Medicinal Products for Human Use gave a positive opinion to Bristol-Myers Squibb's Sprycel (dasatinib) for the treatment of chronic myeloid and acute lymphoblastic leukaemias in patients with resistance or intolerance to prior therapy. The Committee also recommended extending Taxotere's (docetaxel's) indication for use in combination with cisplatin and 5-fluorouracil for the induction treatment of inoperable locally advanced squamous cell carcinoma of the head and neck.

■ European Medicines Agency (www.emea.eu.int)