European School of Oncology
Learning to care

Cancerworld

Number 49, July-August 2012

Education & knowledge through people & facts

Mary Gospodarowicz

➜ Mary Gospodarowicz: Just do it ➜ The patients who are paying a price for Europe's debt crisis ➜ A career dedicated to the most stigmatised group of all ➜ Why your patients may be not be sticking to their prescriptions, and how you can help them do better

Contents

All enquiries about Cancer World should be made to:
ESO Editorial Office
Via del Bollo 4
20123 Milan, Italy
e-mail: magazine@eso.net
Tel: +39 02 8546 4522
Fax: +39 02 8546 4545
All correspondence should be sent to the Editor at editor@eso.net

Cancer World is published six times per year by the European School of Oncology. It is distributed at major conferences, mailed to subscribers and to European opinion leaders, and is available online at www.cancerworld.org

Winning or losing?
ESO asks the experts

Franco Cavalli ■ GUEST EDITOR

Are we winning the war against cancer? This is the provocative title of the World Oncology Forum (WOF), which will take place in Lugano, Switzerland on October 25–27, to mark the 30th year of the European School of Oncology. Rather than hosting a party or a more conventional symposium, ESO feels this is the right moment to tackle some of the big questions the cancer community needs to address. Researchers, directors of cancer institutes, policy makers, chairpersons of professional and research organisations, and representatives of pharmaceutical companies, patients organisations, and international organisations such as the WHO – 80 experts in total – will gather together for two days of intense discussion. A special feature of WOF will be the participation of 20 scientific journalists who will play the role of devil's advocate, challenging the logic and the evidence for the propositions put forward.

Our understanding of the biology of cancer has improved tremendously in recent years, opening many avenues for new treatments that could work better. But how much of the progress that we seem to have achieved with targeted therapies and so-called personalised medicine is really being translated into better outcomes, and how much is hype? What can we do about the rapidly rising number of cancer cases and deaths in low- and middle-income countries, where options for prevention, early diagnosis and treatment are so limited? Many of these countries spend only around $50–100 per person on health every year, while the cost of the latest targeted therapies in rich countries averages $150,000 per patient per year. Can we develop sustainable treatment options? These are some of the questions we will be debating at WOF.

Will we find answers? This is a very complex topic, which may be the main reason why last September's UN Summit on non-communicable diseases, which recognised the huge and increasing burden of cancer worldwide, failed to come up with precise commitments and deadlines. WOF will carry this discussion further, helping to sharpen the focus and the boundaries of this extremely important debate. We are proud to have the cooperation of *The Lancet*. Its editor-in-chief, Richard Horton, will lead the final session, where he will ask the conference to weigh up the arguments heard over the two days and answer the question: "Are we winning the war against cancer?" I'm sure I'm not the only one who is eagerly awaiting the verdict.

Franco Cavalli is the Chairman of the World Oncology Forum and ESO Scientific Committee

Mary Gospodarowicz: Just do it

Marc Beishon

Implement guidelines, adopt what works and reject what doesn't, focus on cost-effectiveness – there are so many ways cancer care could be improved without waiting for the next scientific breakthrough. Mary Gospodarowicz, believer, pragmatist and 'raving optimist', is determined to make it happen.

Last year, the United Nations General Assembly met to set a new international agenda for non-communicable diseases, including cancer. It was only the second summit of its type with a health focus, and the global health leaders who attended heard that these diseases – which also include diabetes, heart disease and others – are growing at an 'astonishing' rate in low- and middle-income countries.

Special mention was made of the economic burden of cancer, which had been flagged up by a World Health Assembly resolution on cancer prevention and control in 2005, prompting the World Health Organization to embark on a cancer control strategy, together with its cancer research body, the International Agency for Research on Cancer (IARC).

Welcome though these developments are, what is remarkable is how long it has taken the major international agencies to recognise the global scale of cancer, and how much responsibility continues to lie with the Union for International Cancer Control (UICC), the long-standing global non-governmental organisation. As its incoming president, Mary Gospodarowicz, a radiation oncologist and medical director at Princess Margaret Hospital in Toronto, explains, the UICC is the only international cancer organisation that aims to bring together the wide variety of players "needed to achieve real improvements on the ground". They include not only cancer control agencies such as the Centers for Disease Control in the US, Cancer Care Ontario and the Cancer Council of Australia, but also all the professional organisations such as ASCO, ESTRO and ECCO; cancer institutes such as Dana Farber in Boston, Tata Memorial Centre in Mumbai, National Cancer Research Centre in Japan; NGOs such as the American Cancer Society and Association of European Cancer Leagues; plus centres and organisations in low- and middle-income countries such as the Ocean Road Cancer Institute in Tanzania, Nigerian Cancer Society, National Cancer Institute in Chile and others.

"It's difficult to lead such a diverse organisation," she says with much understatement. "There is so much need. But following the UN summit we have a big opportunity, now that everyone is recognising that cancer is not only about research and new knowledge but also about applying what we know to trying to improve outcomes worldwide. I'm

passionate about getting UICC engaged in promoting what is now called 'implementation science' – helping to improve cancer control in a cost-effective way that is appropriate to existing country resources."

The UICC is also in a special leadership position, because it is able to take a more political standpoint than governmental organisations such as the WHO, which is part of the UN, adds Gospodarowicz. "We can, for example, push governments to commit more funds to cancer. And we have a long-standing reputation around the world; our brand is our biggest asset. We also have a tremendous network of volunteers who contribute their expertise without any expectation of financial compensation."

The challenge, she says, is how to move UICC's agenda towards the practical 'delivery side' outputs that can really make a difference, and that is not proving to be at all easy. As she points out, the UICC itself has only recently begun to change to a more modern organisation with a vision to attract the right partnerships to determine, and help roll out, what works in cancer control.

"Our core mission hasn't changed – to eliminate cancer as a major cause of death and suffering – and we produced our own set of targets for 2020, with the World Cancer Declaration. These are, however, very broad and cover the full spectrum of cancer issues."

The organisation, she says, is now trying to take a more targeted approach. "In the past few years, we have segmented our constituency to talk to different groups such as cancer control agencies, advocacy organisations, research and treatment organisations and patient support groups, and identified priorities across three main activities – advocacy, 'convening' and programmes. We have been very good at advocacy – we are known as the voice of cancer globally, while convening is about having meaningful congresses and meetings to preach our cause. And we are focusing on a number of specific programmes."

Those programmes include My Child Matters, an initiative to boost paediatric cancer cure rates. "A good way to convince people about the value of cancer work is to cure children – the treatments are often inexpensive and effective and kids will go on to live long lives and it is all highly emotional." Another

WARREN TODA

important programme is the Global Access to Pain Relief Initiative (GAPRI), run jointly with the American Cancer Society, which is attempting to increase the use of opioids to tackle the huge burden of pain suffered in many countries. The third project highlighted by Gospodarowicz focuses on increasing awareness and resources for cervical cancer. It almost goes without saying that tobacco control is also a major concern and needs constant attention as the most important focus for cancer prevention.

There are plenty of other projects, as set out on the UICC's website, but Gospodarowicz is the first to point out that the organisation has limited resources, and a reorganisation to improve its impact on the delivery side is in its early stages. The UICC, she says, has a current budget of only about $10 million and a staff of about 30 based in its office in Geneva.

It was not until 2006 that the major push to modernise UICC started, due to the efforts of John Seffrin, then UICC president and chief executive of the American Cancer Society. What's happened since is a more streamlined approach for priorities and programmes, a radically different model for the two-yearly congress, and an injection of new blood into the Geneva HQ.

This year's world congress takes place in Gospodarowicz's home country, Canada, in Montreal – the third conference held under the new model, following those in Geneva, Switzerland (2008) and Shenzen, China (2010). There are also yearly World Cancer Leaders meetings.

Engaging the right mix of professionals, politicians and patient advocates she sees as critical, and while the internet will become a growing force in communication, meetings focusing on implementation and the patient agenda are now the priority, rather than medical topics, which tended to dominate in past years. "We don't need experts talking about new breast cancer drugs or radiation treatment for prostate cancer – that's being done elsewhere. What we want is people talking about what works in implementing population-based cancer plans, screening programmes, cost-effective treatments and so on.

"Part of the problem is that western countries believe they don't need the UICC because they think they have their cancer control issues figured out. The perception is that the organisation is for developing regions, which in turn don't want developed countries telling them what to do. What developing countries want is partnership, and they like the UICC because they are equal partners in it. But we must become more relevant to western countries, otherwise we become just another missionary organisation."

By no means have developed countries worked out all their cancer issues, she adds, noting large variations in care – particularly in remote areas – high costs, and outcomes that in general are not all they could be. "The barriers to good cancer care are not necessarily just about money – some rich countries spend a lot and worry about sustainability of their systems, which is an incentive for them to engage with the UICC."

A number of professional societies, she adds, have been uninterested in the work of the UICC because of their focus on new, expensive treatments and the inward-looking protection of their members' interests, an attitude she counters in a typically robust style: "My message to colleagues

UICC – A TRULY GLOBAL BODY

The UICC (www.uicc.org) was founded back in 1933, and today has about 400 member organisations in 120 countries. It is based in Geneva.

This year UICC's biannual world congress is in Montreal on 27–30 August. The theme is 'connecting for global health' and programme tracks are prevention and early detection, cancer care and survivorship, palliation and pain control, and systems in cancer control.

A general assembly meeting will also be held in Montreal, at which Mary Gospodarowicz will be confirmed as UICC president for two years. The annual cancer leaders meeting is on 27 August – this is an invitation-only event that has run since 2006.

The UICC is the lead for World Cancer Day, which takes place in early February. The organisation also partners with agencies such as GAVI on other events, such as World Hepatitis Day.

Another important global agency that partners with the UICC is PACT (Programme of Action for Cancer Therapy), an initiative of the International Atomic Energy Authority aimed at helping low- and middle-income countries mobilise resources and funding for cancer prevention, cure and care.

There's a long-standing fellowship programme – currently, about 100 fellows are supported by the UICC each year in activities such as gaining experience at another centre or carrying out bilateral research projects.

"We want people talking about what works in cancer plans, screening, cost-effectiveness and so on"

is: get to the table – it's not about you, it's about the patient. There are plenty of doctors who work in NGOs and health ministries who do work with us. We want the UICC to be broad enough to include all involved in cancer."

Meanwhile, at the UICC's Geneva HQ, a number of new people have joined in full-time capacities, including a new chief executive in 2009, Cary Adams, who came from the banking sector. "We certainly felt we needed a more business-like approach in the office and in our relationships with other organisations. He refreshed the Geneva team and brought new talent to the UICC. There is new energy in Geneva and while the new aggressive agenda can create some tension, it is a creative tension." The UICC's board has also been going through a refresh, and nearly 80 people have been nominated for recent vacancies, which is a very encouraging sign, she adds.

At stake, Gospodarowicz says, is the opportunity to do much more immediately with existing knowledge – "achieving the achievable" as she puts it. "Even with no new discoveries we could increase cancer survival by at least 20%. We know so much more now about prevention and early detection – who would have thought 20 years ago that cervical cancer was induced by a virus, for example?" A recent *Lancet Oncology* review found that one in six cancers worldwide are caused by viral infections.

"People complain that the outlook for cancer is not good – but in the US, incidence and deaths are going down and the warnings that new conditions and drugs will bankrupt us just has not happened. I remember when AIDS came to Toronto; people said the healthcare system would collapse. It didn't. In the 1980s some said new drugs for prostate cancer would bust the budget. Not so. I'm known as a raving optimist – and I think any cancer doctor who is not should get out of the business. The last thing a patient needs is a pessimistic cancer doctor."

WARREN TODA

Such energy and sense of urgency can make some people in well-established organisations uneasy, she admits. "Change in a worldwide organisation is delicate, but you have to take risks to move forward."

Her own way to the presidency was paved by high-level success in her Toronto base together with her long involvement with the development of the TNM cancer staging classification – the globally recognised system for staging cancers, which has long been a UICC project and gained the organisation strong recognition.

She was born in Poland and started medical school in the country before moving with her family to Toronto, where she completed her MD. She went into oncology simply because a job came up – Canada was then

"We went from being several years behind to the forefront by lining up the funding and the right people"

short of trainees – and Gospodarowicz went on to become a clinical oncologist, with board certification in internal medicine, and both medical oncology and radiation oncology. She chose to practise in the latter.

The first ten years or so were spent juggling family life with her career. "It was very important for me that I had a good home–work balance," she says, adding that Princess Margaret Hospital, the cancer centre where she has spent her career, was at the leading edge of radiotherapy for a long spell. "I worked with some amazing people and we had great opportunities to carry out clinical trials and international work. Progress in radiotherapy has been so rapid – today I don't do anything the way I used to when I started out."

Gospodarowicz is now heavily involved in administration, being not only medical director of Princess Margaret, but also heading radiation medicine, chairing radiation oncology at the University of Toronto (she is now at the end of a 10-year spell) and holding the post of regional vice president for Cancer Care Ontario. She was instrumental in putting the case for modernising radiation oncology when it was clear Ontario risked falling behind.

In a textbook example of how to put a case to decision makers, she and her colleagues drew together the evidence for patient need, the optimum level of new technology, and where the field was heading. "They listened and saw the clear evidence, say, for IMRT for head and neck cancers in improving quality of life, which was a starting point for setting targets for patients treated with new equipment. We went from being several years behind to the forefront by lining up the funding and the right people – such as recruiting a world-class medical physicist, David Jaffray – at the right time. Together we led tremendous change. It was very satisfying."

Today Princess Margaret has one of the world's largest radiation oncology programmes, she adds. The total numbers are impressive – over 40 radiation oncologists, 50 medical oncologists, 60 cancer surgeons, and 18,000 new patients a year, mainly from the Toronto area. It is also the largest oncology training centre in Canada.

Gospodarowicz talks excitedly about the latest research and technology agenda at Princess Margaret and in Toronto, such as a major stem cell and a regenerative medicine programme. While stopping uncontrollable cancer cells from developing is one aim, using normal stem cells to repair damage from therapies is another. TECHNA, a new institute for the advancement of health technology created by David Jaffray, and associated with the University of Toronto, aims to bring technologies such as image guidance, nanotechnology, information technology and robotics to healthcare. "It is one of the few such projects in the world and it is very exciting," she says.

Advances could also impact on intractable problems in her own fields of prostate cancer and lymphomas, such as new image-guided treatment approaches. Princess Margaret has a good track record, she adds, in redefining treatment standards, having for example persisted with work on stopping radiotherapy for stage I testicular cancer and opting instead for surveillance, which is now widely accepted. Another challenge is how to assess the long-term outcomes typical of diseases such as Hodgkin's, which is a particular interest for her. She is especially proud of her long-term participation in international cooperative group trials, three of which – on prostate, bladder and Hodgkin's – were well-received last year.

As a senior director in cancer care, she has come to some pragmatic views about the organisation of care, particularly among doctors. A multiple-trained specialist herself, she feels that the lines between specialties are becoming more blurred. Interventional radiologists, she feels, are closer to surgeons than to other radiologists, while in smaller centres patients may be better served by surgeons who are 'dual trained' in surgery and chemotherapy, rather than having care provided by two separate doctors – surgeon and oncologist. "It's good to have one doctor if you are a patient having straightforward

chemo- or hormonal therapy," she says.

Models of multidisciplinary care should not be too rigid, she feels. "We have tried systems where patients are seen by a large number of specialists, and it can be very wasteful. The issue is trust – for example, that I will not miss an opportunity to discuss surgery as a radiation oncologist. But then all team members need a high level of competence – not just superficial knowledge. It's about being patient-centred and cost effective. I've heard that some physicians no longer want to make decisions, and leave them to a group decision at a tumour board, which hasn't seen the patient. We shouldn't abdicate our responsibility to a committee."

If Gospodarowicz had her way, it would be drummed into medical school students that healthcare is a business and that principles that work in other industries, such as standardisation, improve quality. "If people knew that, they would treat guidelines differently, and not as an infringement on professional freedom. Cancer Care Ontario now collects data on the proportion of patients treated according to evidence, and the adherence to guidelines is suboptimal. But at Princess Margaret, as a research centre, we do have many patients on trials outside of guidelines to create new evidence."

In fact, she adds, Cancer Care Ontario can now match every patient on its registry with every drug, radiation fraction and surgical procedure, so that outcomes can be reported by tumour site, and staging data are available for 90% of all new cancers. "Although it is new and we are still working on how and what to measure, if we can do it so can others – and it's just the sort of model that we want to share with UICC members."

WARREN TODA

Underlying this work is the fundamental issue of how tumours are classified, and the TNM staging protocol that first brought Gospodarowicz into contact with the UICC, as the Canadian representative on the TNM committee. As she describes, as a young oncologist she had found that there were

"Some physicians no longer want to make decisions, and leave it to a tumour board, which hasn't seen the patient"

The report makes the point that countries get richer if they invest in cancer care

several different staging systems in testicular cancer, some of them promoted only by a single cancer institute, but a consensus emerged and was translated into the TNM system, which has now been in use for over 60 years.

"I naively thought there was an international organisation responsible for such medical standards," she says, noting that although the UICC is the custodian of TNM, the effort and continuity depends on volunteer support. "It's also the case that the other main classification – that of the disease itself, or pathology – has at times had variable international support. While IARC has managed this as a WHO classification, there is no international organisation that has formal responsibility. I found this mind-boggling when I started out as an oncologist."

This matters a lot because, without strong and consistent support, tumour classification, and TNM in particular, is subject to much misconception and competing interests, Gospodarowicz says, and its value can be diluted. "One problem is that people want to mix the anatomic extent of disease, or stage, with the type of disease (tumour profile), but that's not a staging classification, it's a prognostic classification. It is a terminology debate."

The two can certainly be combined as a prognostic classification – 'cancer staging' with 'tumour profiling', including also the patient's characteristics – age, comorbidities and so on, which also determine treatments and outcomes. "This is what people don't talk about: all prognostic classifications depend on the intervention and what you can apply – a stage I cancer could be fatal or curable. A staging classification tells you how much tumour there is and where it is – you just describe what's present. I feel passionately that we shouldn't be discarding a common language for oncologists that's been around for 50 years."

It's not that TNM is standing still – it's now in its 7th edition and its proponents recognise the need to integrate non-anatomic prognostic factors, but in a way that leaves the underlying values of TNM intact, so it can remain as a worldwide standard for comparing population groups, and stratifying patients into similar groups, which is important, for instance, to allow meaningful clinical trials to be conducted.

Gospodarowicz says the argument is hard to win, with on the one hand, pressures for introducing more complexity from those impatient to push advances in molecular biology into the system, and pleas from cancer registries to actually have a simpler staging classification on the other.

Naturally, medical oncologists generally do not require TNM as a tool for selecting systemic therapy, but TNM is crucial for radiation oncologists and surgeons, who deliver local therapy, she says. TNM has come under particular fire from breast cancer specialists in the West, where a vast majority of patients present with early-stage disease, so TNM alone is not good enough and they need other tools. "But around the world TNM is one of the strongest predictors of outcome – there seems to be an innate desire to change the language," she says, adding that consensus tends to be an undervalued commodity.

The agenda for the UICC's Montreal congress is firmly directed at ways to develop consensus and decrease inequality, and Gospodarowicz is hoping that strategies to engage more global leaders will pay dividends. One piece of work she cites that has helped set the agenda is the report from the Global Task Force on Expanded Access to Cancer Care and Control in Developing Countries, of which she was a member, and which was led by Felicia Knaul from the Harvard Global Equity Initiative, and which brought together many of the cancer and healthcare world's leading lights.

The report, 'Closing the Cancer Divide… a blueprint to expand access in low and middle income countries', is extremely important, says Gospodarowicz, because it combines the cause of cancer with economics. "It calculates how much cancer costs and makes the point that countries get richer if they invest in cancer care. It's a no-brainer that we need to engage with smart people like

MARKO SHARK

The gold standard. Gospodarowicz with colleagues, a solid gold bar and its escort of Canadian mountees, at the April launch of the Believe it! campaign to raise one billion Canadian dollars to accelerate personalised medicine at the Princess Margaret hospital in Toronto

those at Harvard and amplify their voices."

Although rich countries could achieve much more with existing resources, there is clearly a need for more investment in low- and middle-income nations, and the UICC's role in fundraising is very much on Gospodarowicz's agenda. "We do have industry financing for some of our programmes, but we need to do much more with other organisations. Targeting philanthropists is difficult – you need a skilled execution body to create the tight proposals that agencies such as the Gates Foundation will act on. We need to capitalise more on our partnerships with WHO and IARC, and others such as GAVI, the global vaccines agency."

So much more could be done in particular with electronic communications such as mobile health systems (m-health) in developing countries, she says. "The Internet is an amazing equaliser – I now have patients in my clinics who know more than I do. You either fight or embrace it. ICTs [information and communication technologies] should make a huge impact on healthcare and they are part of our new TECHNA institute."

A project that she encouraged to develop in Canada is ELLICSR, a cancer survivorship laboratory that includes a virtual, online support community. "We don't know how people will engage with systems like this – it's still experimental but it's really not very expensive."

For Gospodarowicz, change can't come fast enough, be it in ICT, implementation science or new roles for healthcare professionals – on the last subject she gave a talk last year at the Center for Global Health at the US NCI (itself a welcome new programme) on the need for a rethink on the way that human resources can meet patient needs.

No doubt her family, husband David, a urologist and coroner, and her two children – who have their own rich careers and have not followed their parents into medicine – are well served by all this energy.

Meanwhile, a test of her input into fundraising – and optimism – has recently been set in train by the Princess Margaret Hospital Foundation, which aims to pull in a cool billion dollars (Canadian) for personalised cancer medicine, under the banner, 'Believe It: we will conquer cancer in our lifetime'. "It's a huge effort, but we will raise the funds and be successful."

New accomplishments in breast cancer chemoprevention

Too toxic, too untargeted, too difficult to prove. These assumptions about chemoprevention are being challenged by important developments in the search for preventive options tailored to specific risk factors in breast cancer.

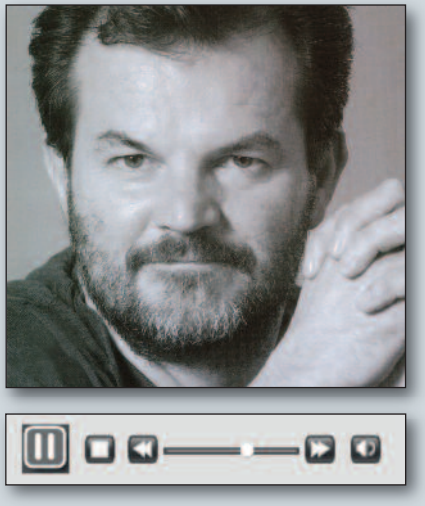
Recent years have seen some important developments in chemoprevention of breast cancer. These include the use of aromatase inhibitors (AIs) for prevention, including the MAP.3 trial with exemestane, and investigations into the best way to use targeted agents in presurgical models, such as lapatinib for HER2-positive ductal carcinoma in situ (DCIS) and metformin in insulin-resistant women who have breast cancer or are at risk of developing breast cancer.

Looking at what we can learn from cardiologists, the mortality rate for cardiovascular disease in the US has fallen sharply over the last forty years compared to a relatively stable curve for cancer mortality. This is essentially due to the efforts cardiologists and other internal medicine specialists have made in the prevention of cardiovascular disease. I think we in the cancer community have to switch our efforts towards early intervention, such as treating at-risk conditions, as the cardiologists are doing with the treatment of hypercholesterolaemia and hypertension, which is translating into decreased mortality.

European School of Oncology
e-grandround

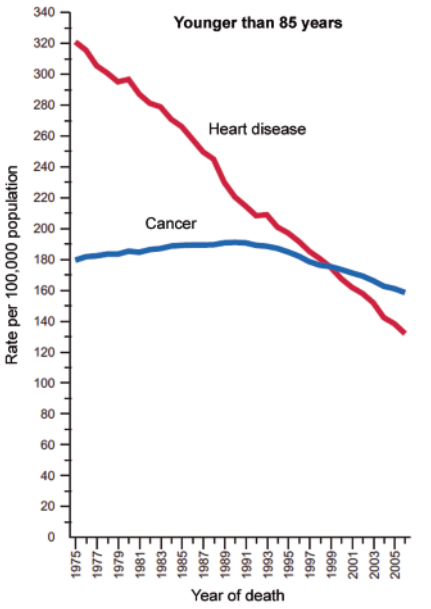
The European School of Oncology presents weekly e-grandrounds which offer participants the opportunity to discuss a range of cutting-edge issues, from controversial areas and the latest scientific developments to challenging clinical cases, with leading European experts in the field. One of these is selected for publication in each issue of *Cancer World*.

In this issue, Andrea DeCensi, of the medical oncology department at Ospedali Galliera, in Genova, Italy, reviews recent achievements in the chemoprevention of breast cancer. Bernardo Bonanni, of the cancer prevention and genetics department at the European Institute of Oncology, in Milan, Italy, poses questions arising during the e-grandround live presentation. The presentation is summarised by Susan Mayor.



The recorded version of this and other e-grandrounds, is available at www.e-eso.net

LESSONS FROM CARDIOLOGY



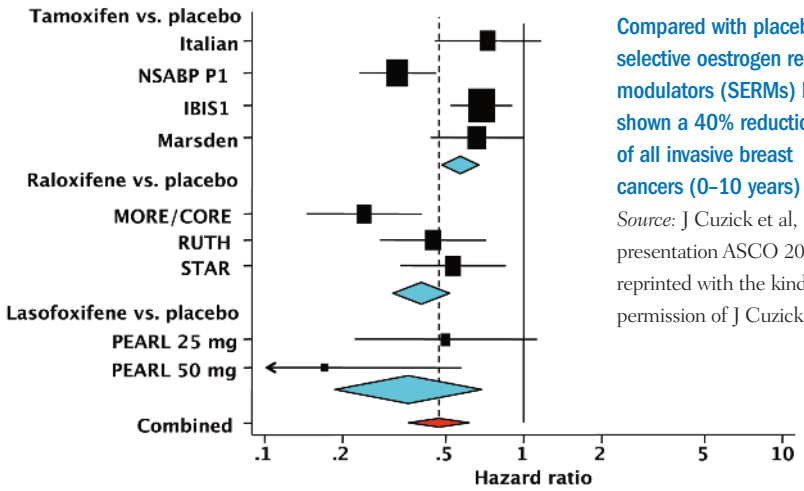
Could strategies for treating people with conditions that raise the risk of cancer lead to the sort of decrease in deaths achieved in cardiology?

Source: A Jemal et al. (2010) *CA A Cancer Journal for Clinicians* 60:277–300, reprinted with permission

Up until publication of the MAP.3 trial, two agents, tamoxifen and raloxifene, have been registered for the prevention of breast cancer in the US and Canada, associated with a 40% reduction in the incidence of breast cancer. A third compound, lasofoxifene, used for the treatment of osteoporosis, is also associated with a very significant reduction in breast cancer (see figure below).

These results suggest we have several very active agents that can be given to women at increased risk for breast cancer, but unfortunately their use is associated with increased risk of important adverse events. Endometrial cancer is increased by 30–40% with tamoxifen and all selective oestrogen receptor modulators (SERMs) are associated with an increased risk of deep-vein thrombosis and pulmonary emboli. These side-effects have limited the broad use of these compounds in the clinical setting. In addition these drugs are not registered outside the US, so their use is off-label in Europe.

PREVENTIVE IMPACT OF SERMs



Compared with placebo, selective oestrogen receptor modulators (SERMs) have shown a 40% reduction of all invasive breast cancers (0–10 years)

Source: J Cuzick et al, presentation ASCO 2012, reprinted with the kind permission of J Cuzick

A TURNING POINT: THE MAP.3 TRIAL

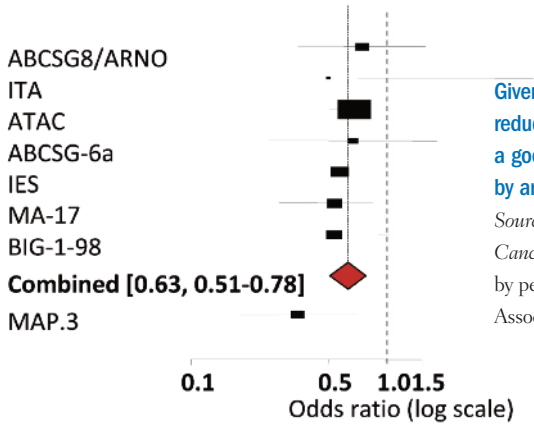
A very important turning point occurred last year (2011) with the publication of the first data from the MAP.3 trial in the *New England Journal of Medicine* (364:2381–91). The study, which investigated exemestane in women at increased risk of breast cancer, was accompanied by a very positive editorial suggesting this was a breakthrough with this new class of agents that may represent an important step forward in the prevention of breast cancer.

The rationale for using aromatase inhibitors (AIs) in breast cancer prevention is derived from their demonstrated effect on contralateral breast cancers. The figure opposite (*top*) shows a Forest plot of the most important adjuvant trials with AIs, which shows clearly that the incidence of contralateral breast cancer, which is a very important surrogate endpoint for prevention, decreased by approximately 40% with all types of third-generation AIs, including anastrozole, letrozole and exemestane. Data from the MAP.3 trial show an even greater reduction in women who were treated for primary breast cancer.

The MAP.3 trial was a double-blind trial that randomised 4560 women recruited from February 2004 to March 2010 to exemestane (25 mg/day) or placebo (1 mg/day) for five years. Study participants were post-menopausal women aged 35 years and older who had at least one of the following risk factors for breast cancer: age >60 years, Gail score >1.66%, prior intraepithelial neoplasia or intraductal carcinoma in the contralateral breast or DCIS with prior mastectomy. There were two stratification factors: the use of aspirin and the level of risk on the Gail score (<2.0 vs >2.0).

The figure opposite (*bottom*) shows the main results of the trial. Starting from the first year there is a very significant

IMPACT OF ADJUVANT AIs ON CONTRALATERAL BREAST CANCERS



Given adjuvantly, aromatase inhibitors reduce contralateral breast cancers – a good surrogate for prevention – by around 40%

Source: A DeCensi et al. (2012) *Cancer Discovery* 2:25–40, reprinted by permission from the American Association of Cancer Research

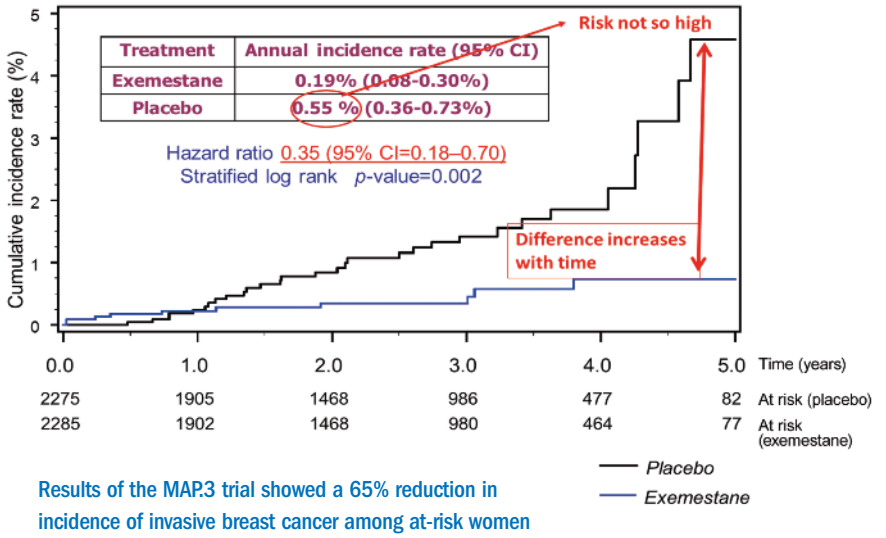
reduction in the cumulative incidence of invasive breast cancer in the exemestane group compared to the placebo group. The curves tend to diverge as follow-up continues. However, the risk in the placebo arm was not as high as was probably envisioned in the study planning – at only 0.55% per year. This is slightly lower than the risk seen in earlier phase III trials – the P1 and P2 trials. The reduction in invasive breast cancer associated with exemestane was as high as 65%, with a hazard ratio of 0.35 that was highly significant (P=0.002). These data show a very remarkable risk reduction in invasive breast cancer with exemestane.

Further data showed that exemestane significantly reduced DCIS in addition to invasive breast cancer (HR 0.47). There was a favourable trend in the reduction of DCIS alone (HR 0.65), although this was not statistically significant due to the relatively small number, and also there was a borderline significant reduction of new intraepithelial neoplasia including lobular carcinoma in situ, atypical ductal hyperplasia and atypical lobular hyperplasia (HR 0.36).

In terms of side-effects with exemestane, there was a significant increase of menopausal symptoms, including hot flushes, fatigue, insomnia, diarrhoea, nausea, arthritis, joint pain, muscle pain, depression and vaginal dryness. But the differences compared to placebo were generally quite limited, and only a minority of women had to interrupt treatment because of bothersome side-effects.

Putting these data into context, one of the main arguments against chemoprevention for breast cancer was that you have to treat a lot of women to prevent a few breast cancers. But, if we look at the data for the MAP.3 trial and use 'number needed to treat' at five years to illustrate the efficacy compared to other interventions, you can see that you have to treat 27 women to prevent one breast cancer. This is highly comparable to the most effective statin intervention, which is illustrated in the Jupiter trial using rosuvastatin (see figure, page 16). The argument here is that, with an effective chemopreventive agent such as exemestane, the reduction in the risk of breast cancer in women at risk is comparable to the reduction in the risk of cardiovascular disease with statins in subjects with elevated C-reactive protein or cholesterol. The specificity or cost–benefit ratio is similar for the best preventive interventions that we have today.

EXEMESTANE: CUMULATIVE INCIDENCE OF INVASIVE BREAST CANCER

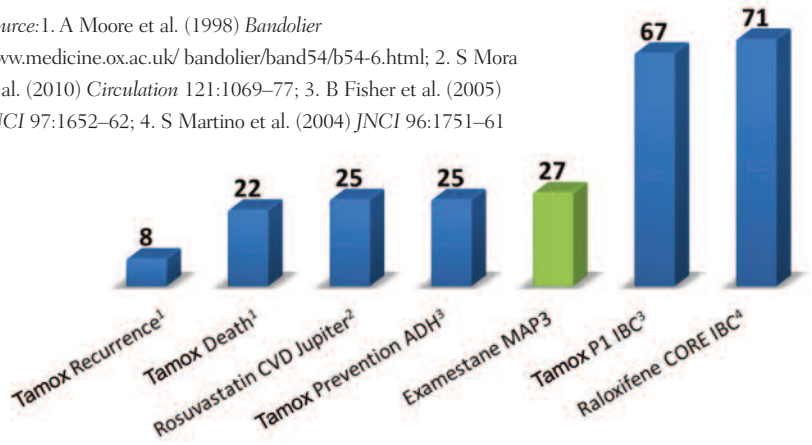


Results of the MAP.3 trial showed a 65% reduction in incidence of invasive breast cancer among at-risk women given exemestane for five years compared with those given placebo

Source: PE Goss et al. (2011) *NEJM* 364:2381–91, reprinted with permission

FIVE-YEAR NUMBER NEEDED TO TREAT

Source: 1. A Moore et al. (1998) *Bandolier* www.medicine.ox.ac.uk/ bandolier/band54/b54-6.html; 2. S Mora et al. (2010) *Circulation* 121:1069–77; 3. B Fisher et al. (2005) *JNCI* 97:1652–62; 4. S Martino et al. (2004) *JNCI* 96:1751–61



These data show that, at five years, the 'number needed to treat' to prevent one breast cancer in an at-risk population using exemestane is similar to that needed to prevent one new case of cardiovascular disease using the most effective statin, rosuvastatin, in an at-risk population

The MAP.3 trial did have some limitations. The definition of 'high risk' has been criticised as rather loose. The trial was also criticised for giving placebo to the comparator group instead of an active compound such as raloxifene, thereby preventing determination of the best hormonal strategy: no oestrogen at all versus the best balance between agonistic and antagonistic effect. However, a study with an active comparator would require a much larger number of patients and the cost would be prohibitive.

A further important criticism of the first paper (*NEJM* 2011; 364: 2381–91) was the lack of systematic follow-up of bone density for osteoporosis detection. The incidence of osteoporosis was self-reported and is likely to be underestimated. A very recent study published in *Lancet Oncology* (2012; 13:275–284) showed that exemestane was associated with significant bone loss at two years in a subgroup of women, as would be expected. This needs to be addressed in any discussion of the pros and cons of a drug intervention, as for any treatment used in the current practice of modern medicine.

Another weak point is the study's maturity, because the data were published after only 38 events had accumulated, and follow-up was very short. Although the study is technically accurate from a statistical standpoint, it does not allow a mature judgement of the safety and long-term efficacy of the intervention. Finally, there is the problem that the study was interrupted and women on placebo were offered crossover to exemestane, so long-term follow-up including mortality data will not be possible.

A NEW STANDARD OF CARE FOR PREVENTION OF BREAST CANCER

We now have a new standard for preventive care in breast cancer: in addition to tamoxifen for women at increased risk who are premenopausal, we now have exemestane (or raloxifene) for at-risk postmenopausal women. Any drug has side-effects, but this is a particular problem in cancer medicine, as any drug that interferes with cell growth is unlikely to be totally devoid of side-effects. The medical oncology community should spread the notion that most breast cancers are preventable today. Although screening has increased the detection of breast cancer at an early stage while tumours are small, there is still a risk that these tumours will eventually kill women.

Exemestane is now out of patent in the US and Europe. This means that no-one will register this drug for prevention, and therefore prescribing it will be off label, which is a barrier with current legislation. Once the efficacy of a drug has been assessed, the time has elapsed for its patent, which then makes it difficult to foster its use in clinical practice. This begs the question: How can we develop new agents to use in prevention before the patent expires?

THE WINDOW OF OPPORTUNITY MODEL FOR EXPLORING THE FIELD CANCERISATION EFFECT

Our group has been working with the window of opportunity (WOP) model over the last few years for presurgical studies three or four weeks before surgery, to study not only the change in biomarkers in malignant tissue but also the change in biomarkers in adjacent intraepithelial neoplasia and distant ductal hyperplasia (see figure opposite, *top*). This model provides an elegant way to reveal the 'field cancerisation effect' – a term used to describe the hyperplasia and precancerous lesions that are present in tissue surrounding an actual malignant tumour.

Immunohistochemistry staining illustrated in the figure opposite (*bottom*) shows that precancer adjacent to the malignant tumour – ductal intraepithelial neoplasia (DIN) – is a frequent finding. In the left upper panel, morphological assessment of the area of DCIS shows the Ki-67 (proliferation

index) is 14%. In the right lower panel, the proliferation index of this area of DCIS is much higher (Ki-67 = 52%).

We assessed the activity of lapatinib, which is a HER1/HER2 tyrosine kinase inhibitor (TKI), in women with HER2-positive breast cancer. They were treated for three weeks with lapatinib or placebo before surgery. We first carried out a core biopsy, then treated with lapatinib or placebo for three weeks, and then performed surgery and looked at the change in biomarkers.

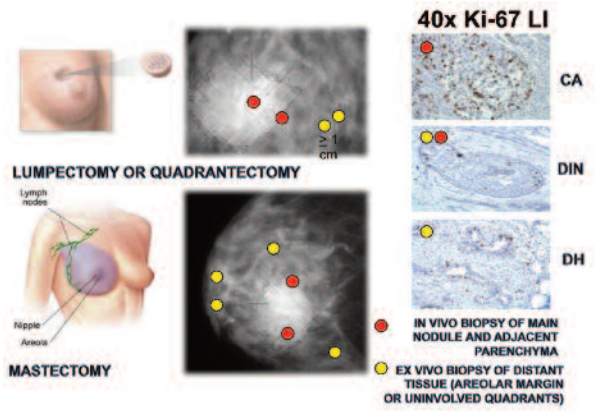
Results in malignant tissue showed an increase in Ki-67 in the placebo arm after surgery compared to the pre-surgery biopsy. In contrast, there was a reduction in Ki-67 in the lapatinib arm, which was highly significant in tumours not expressing oestrogen or progesterone receptors (see figure page 18, *top*).

The most important finding was that the prevalence of adjacent DCIS was as high as 70–76% and the prevalence of distant hyperplasia was over 90%. This presurgical model revealed the high incidence of precursor conditions that are associated with tumour tissue.

A very important question is whether we should use lapatinib for treating HER2-positive DCIS. We know that lapatinib is not as active as other anti-HER2 drugs for the treatment of breast cancer, but because it is an oral agent it may be interesting in the treatment of HER2-positive DCIS after surgery.

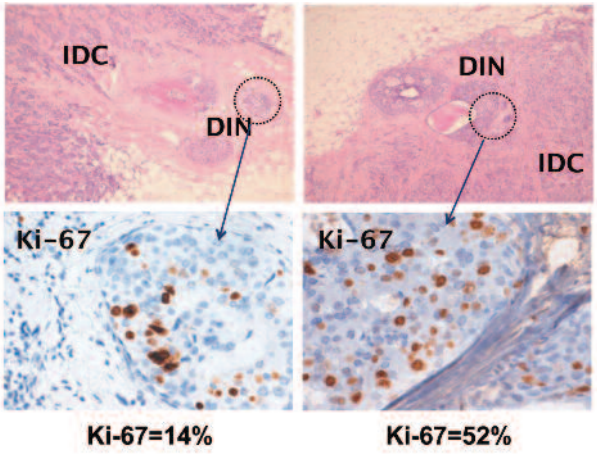
We wanted to understand whether lapatinib was interfering with cancer-adjacent DCIS and whether this cancer-adjacent DCIS was overexpressing HER2 or had an amplified HER2. Results showed that 90% of all HER2-positive cancer-adjacent DCIS overexpressed HER2.

THE FIELD CANCERISATION EFFECT



The 'window of opportunity' (WOP) model allows us to see the impact of treatments not only on biomarkers in malignant tissue (CA) but on biomarkers in adjacent ductal intraepithelial neoplasia (DIN) as well in distant ductal hyperplasia (DH)

PRECANCER IN AREAS ADJACENT TO IDC



It is common to find precancer adjacent to the malignant tumour

IDC – infiltrating ductal carcinoma, DIN – ductal intraepithelial neoplasia

Source: Slides courtesy of Andrea DeCensi

Lapatinib achieved a significant decline in Ki-67 in this premalignant tissue, with the reduction being highly significant in tumours not expressing oestrogen or progesterone receptors. This strengthened our hypothesis that lapatinib could be assessed as an adjuvant treatment after the resection of HER2-positive DCIS, which represents 20–25% of all instances of DCIS.

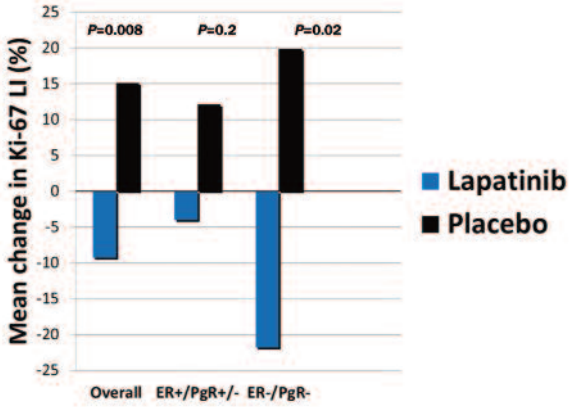
The take-home message was that short-term, pre-surgical treatment with lapatinib decreases cell proliferation in HER2-positive DCIS. We therefore believe that a phase III trial in HER2-positive DCIS is warranted.

Metformin in breast cancer prevention

The potential use of metformin in breast cancer prevention is a very hot topic at the moment. Metformin is an anti-diabetic biguanide, which is used for the treatment of non-insulin-dependent diabetes. It is also used for the treatment of polycystic ovary syndrome in non-diabetic women. This syndrome occurs in young women and is associated with insulin resistance.

Metformin is a safe drug used by millions of people around the world. The rationale for its use in cancer prevention and treatment is that obesity is an independent risk factor for postmenopausal breast cancer. Hyperinsulinaemia – reflecting underlying insulin resistance, which is reversible with metformin – is a likely mediator of this effect. Insulin has an independent role in breast cancer development.

CHANGE IN Ki-67 FROM BEFORE vs AFTER SURGERY



Lapatinib given for three weeks prior to surgery for HER2-positive breast cancer led to a highly significant reduction in the proliferation rate (Ki-67) in cancers not expressing oestrogen or progesterone receptors

Source: A DeCensi et al. (2011) *Cancer Prev Res* 4:1181–89

Recent data from epidemiological studies have shown that metformin can reduce the incidence of several cancers compared with other anti-diabetes agents. There are two main mechanisms attributed to metformin for this cancer preventive effect. One is an indirect effect through insulin and the second is a direct effect on tumour cells through a number of different pathways that essentially converge in the mTOR pathway (see figure below).

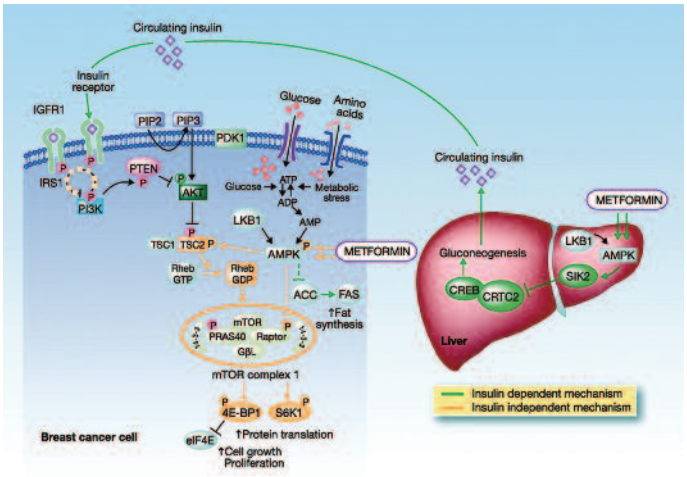
A very recent study from our group showed that in a Forest plot of all studies with metformin in breast cancer, the drug was associated with a small but significant decline in breast cancer incidence compared to anti-diabetic drugs, namely insulin and sulfonylureas (relative risk 0.94). One argument is that the comparators may increase the risk of breast cancer, so it is very important to carry out clinical studies to determine whether metformin has an anti-tumour effect per se.

Using our pre-surgical WOP model, we recently completed a study in 200 women with breast cancer who were treated for four weeks with metformin or placebo before surgery. We looked at the change in Ki-67 as the primary endpoint and also whether there was a different effect according to hormone receptor status and insulin resistance status.

A pivotal trial that was conducted ten years ago, the Diabetes Prevention Programme (*NEJM* 2002, 346:393–403), which was a primary prevention trial of metformin in subjects at risk for diabetes, showed that both lifestyle changes (namely diet) and metformin were able to decrease the incidence of diabetes. What is very relevant to our discussion here is that the effect of metformin was much greater in women who were obese, or overweight, and in those who were insulin resistant, in that they had pre-diabetes glucose levels. So, we already had important information that the effect of metformin is dependent on the metabolic milieu of the host.

The main finding of our study (*JCO*, published online 7 May 2012) was that there was no modulation of cancer proliferation overall (see figure opposite). There was a small trend to increased Ki-67 in the whole population, but this was not significant. When we stratified subjects according to insulin-resistant status, by the HOMA index, there was a different effect, with a trend to decreased proliferation in women with insulin resistance, as shown by the increase in the HOMA index >2.8. There was the opposite effect in women who were not insulin resistant, who made up the majority of the study

IMPACT OF INSULIN AND METFORMIN ON BREAST CANCER



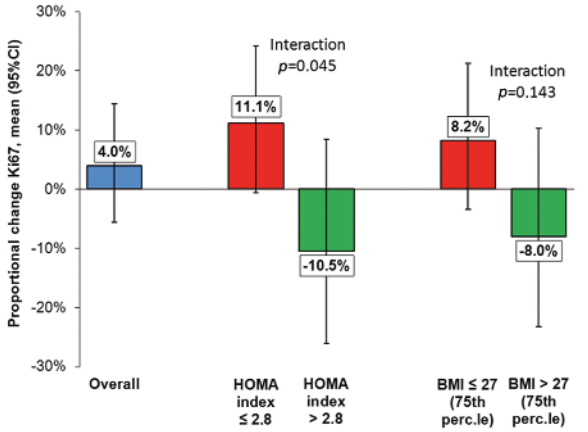
Source: AM Gonzalez-Angulo et al. (2010) *Clin Cancer Res* 16:1695–1700, reprinted with permission

The anti-diabetic drug metformin exerts a preventive effect on several cancers by acting directly on tumour cells and indirectly through insulin

population, with a trend to an increase in cancer proliferation. This is very different behaviour, which is represented statistically by a significant interaction that means that the HOMA index modifies the effect of metformin on cancer proliferation. A similar pattern was seen with body mass index (BMI), so women who were overweight or obese showed a decrease in cancer proliferation as opposed to an increase in women of normal weight. These findings completely resembled those of the Diabetes Prevention Programme.

In conclusion, the take-home message here is that metformin given for four weeks prior to surgery reduced breast cancer proliferation in women with insulin resistance or with a BMI >27 kg/m^2. There was an opposite trend in patients with normal insulin sensitivity or normal weight. We think that our study is very important because it proves the principle that metformin can be effective in women who have certain metabolic disorders that predispose them to an increased risk of breast cancer, namely insulin resistance or obesity. Metformin should not be recommended in older women without these metabolic disorders. A phase III trial with metformin is underway in women regardless of their BMI or insulin resistance status, but our data suggest a need for careful consideration of the study population.

EFFECT OF METFORMIN ON PROLIFERATION INDEX



Giving four weeks of metformin to breast cancer patients prior to surgery showed that insulin resistance, defined according to the HOMA index, modifies the impact of metformin on cancer proliferation in a statistically significant way

Source: B Bonanni et al (2012) *JCO* published online 7 May 2012

Q&A

Bernardo Bonanni (BB), of the cancer prevention and genetics department at the European Institute of Oncology, in Milan, Italy, hosted a question and answer session with Andrea DeCensi (AD)

BB: *Your take-home messages are very clear, but to get an even broader message, do you think we are approaching more targeted prevention treatment, at least in some at-risk subgroups?*

AD: We live in an era of personalised medicine, and I think that prevention should follow this avenue of going towards personalised preventive therapy. We have shown a couple of examples where we can target a specific population with two interesting compounds. In the first example, we have an agent such as lapatinib, which can be used to reduce the risk of recurrence in women with HER2-positive DCIS. This is a specific population where a drug can be extremely effective.

The second example is metformin, which can be used for reducing the risk of breast cancer, or for treating breast cancer after surgery in an adjuvant setting, in women with certain metabolic characteristics, such as the presence of insulin resistance or obesity. In this second instance, the population at risk is much larger, especially in Northern European or in the American countries.

BB: *How do you see oncologists moving closer to cardiologists in successfully spreading prevention of breast cancer among the wider public?*

AD: This is a very tough question. We should probably put less emphasis on the potential toxicity of drugs, which is intrinsic to drug treatment. I read with some disappointment the editorial in *Lancet Oncology* on the bone toxicity of exemestane. It gives the impression that osteoporosis is equal to breast cancer, which is absolutely not the case. We cannot compare a breast cancer prevented with a case of osteoporosis induced. The second is very easily manageable with drugs today; it is not even a disease but a risk factor. In contrast, even a small breast cancer can still be lethal. I think one approach for spreading prevention is to not give so much emphasis to the potential toxicity when you have a drug like exemestane, which is extremely effective in preventing two-thirds of breast cancers.

Breaking boundaries

How Jean-Louis Lefebvre has been making life better for the most stigmatised of cancer patients

➜ Simon Crompton

Often mistaken for a radiotherapist or medical oncologist, this expert in voice-box sparing strategies has reached out to a wide variety of professionals – most recently actors – in his quest to improve the chances of patients with head and neck cancers.

It's fitting that one of the world's most influential specialists on cancers that threaten speech shows a rare understanding of the importance of good communication. Jean-Louis Lefebvre, president of the European Head and Neck Society, worries before our interview that I will not be able to make sense of his 'French English'. In fact he's direct, clear and concise. But his concern reflects a knowledge that the way we use words is at the heart of good clinical care.

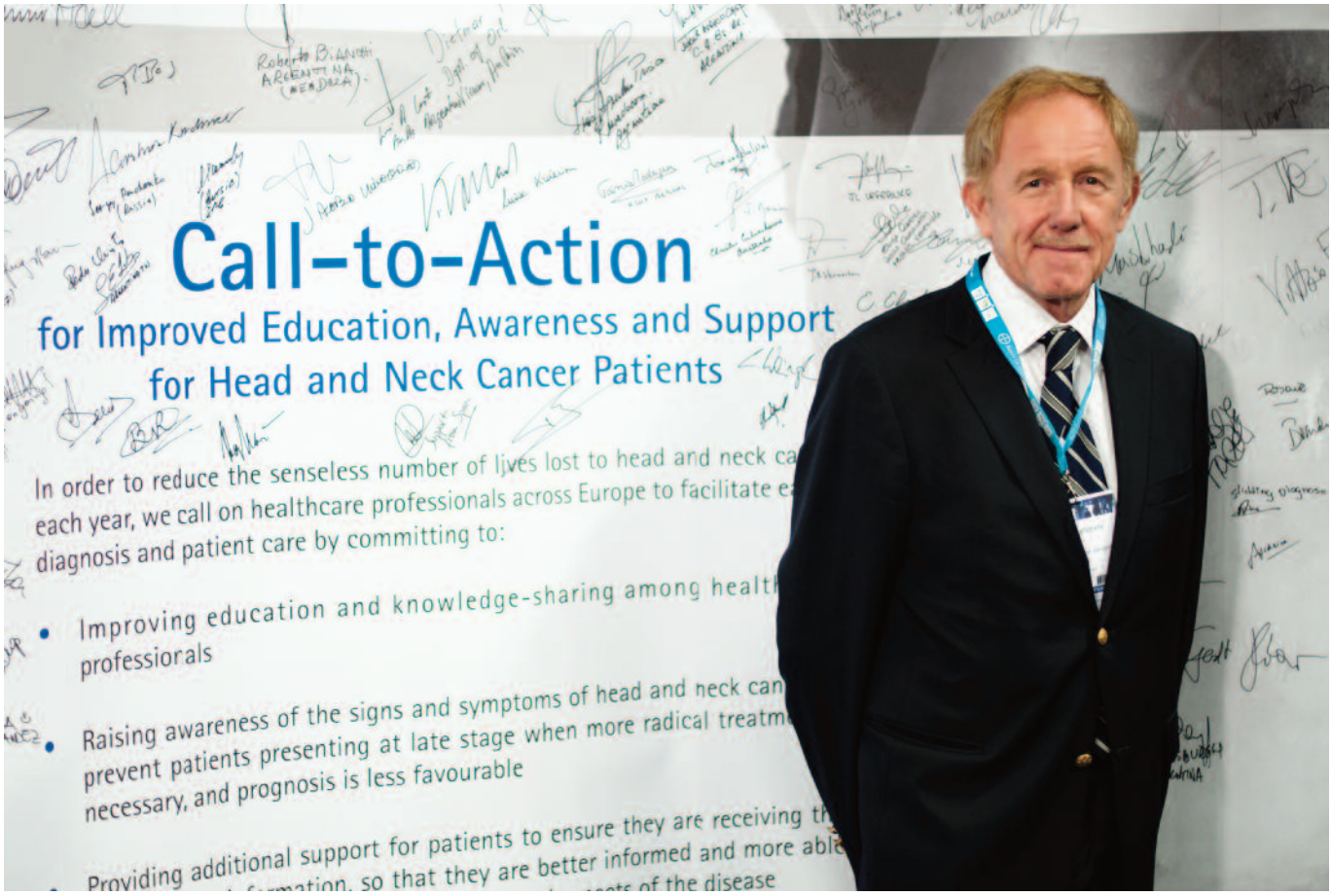
For patients with head and neck cancers – who often come from marginalised sections of society and are unfamiliar with healthcare systems – it's completely fundamental says Lefebvre, who has been chief of the Head and Neck Department of the Centre Oscar Lambret at the Northern France Comprehensive Cancer Center in Lille since 1978.

"Because the disease is often advanced, you're having to talk through with them complex combinations of therapy, talking about PET scans, MRIs, CT scans, biology and endoscopy, often when they're still in shock after being told they have cancer. 'Hospital' is a new and strange word for them. This is a completely different situation than breast cancer, where many women are already well informed through the internet and in magazines. They know they need scans if they have cancer."

Risk factors for head and neck cancers include heavy tobacco intake, often associated with alcohol abuse. More recently, a link has been uncovered between some types of head and neck cancers and the HPV virus, so oral sex is now believed to be a risk factor too. The result is that the subject is unglamourous and difficult for the media and health information campaigns. It is hardly surprising, then, that two-thirds of head and neck tumours are diagnosed late, and neck tumours are on average 3–4 cm at time of diagnosis.

Lefebvre, a surgeon who has become one of the world's authorities on larynx preservation and multidisciplinary approaches for head and neck cancers, has defined the recent years of his career with initiatives encouraging better understanding of the reasons for late diagnosis and better public awareness for these most unsexy of cancers.

This was manifested most dramatically at last year's European Multidisciplinary Cancer Con-



AEON VERLAG & STUDIO

Advocate. Lefebvre has led efforts to raise public awareness about head and neck cancers and improve professional understanding of the particular needs of this group of patients

gress in Stockholm, where the European Head and Neck Society presented a play, as part of a satellite symposium, about the patient journey. Performed by professional actors, it told the story of Brian – an irascible former businessman, now separated, alone and bitter – who spends his days drinking, smoking and gambling. He is gradually persuaded by his estranged daughter that he should see a doctor about his swollen throat and persistent coughing. There is a telling scene where Brian is told he has cancer and immediately retreats into himself, oblivious to his daughter's caring enquiries and the doctor's technical monologue about oropharyngeal tumours, MRIs, ENT and being referred to specialists.

The play, the product of a collaboration between the European Head and Neck Society and pharmaceutical company Merck Serono, was titled *Senseless* "because of the senseless number of lives being lost through late diagnosis and lack of awareness," says Lefebvre.

This is not a group of people that are always easy to help, nor do they go out of their way to help themselves. But over his 40-year career, Lefebvre has gone way beyond the role of the surgeon to try to address this. For virtually all that time – apart from brief spells at the start of his career in hospitals in Houston and New York – Lefebvre's place of employment has been within a square kilometer in Lille, a city in the North of France where the incidence of head and neck cancer is among the highest in Europe. From his office in the Centre Oscar Lambret, he pulls aside a blind to reveal an imposing 1950s block a few hundred yards away that looks

"The patient stays in the same department, with different professionals revolving around them"

like something from George Orwell's *Nineteen Eighty-four*. That, he points out, is the University Hospital where he started work as a surgeon.

He was born not far away too, in 1947 in Valenciennes, 40 km south of Lille. Lefebvre's father died when he was young, and his mother hoped he would become an engineer. But unable to get fired up by maths and physics, he went to medical school instead. At the end of general training at Lille University, his interest in plastic surgery led him to the Ear Nose and Throat Department at the University Hospital. It was there that he rapidly developed an interest in head and neck cancer.

"After studying medicine I knew nothing about head and neck cancer and wanted to know more," he says. "We'd had less than 20 hours in total on ENT, which is nothing – so I knew head and neck cancers existed, but not much more."

What happened at the University Hospital between 1970 and 1974 set the tone for the rest of his career. Early on in our conversation, Lefebvre takes out of a cabinet a small framed picture of the man he describes as "my mentor", and props it in front of me. It is Jean-Jacques Piquet, then head of the ENT department at the University Hospital. With Piquet, Lefebvre worked on a new technique of partial laryngectomy, which gave some patients with larynx cancer the option of retaining part of their larynx (voice box) and avoiding a permanent tracheostomy (opening in the neck for breathing).

Through Piquet he also started to learn about the importance of other disciplines. "Every Wednesday afternoon, a radiation therapist from this hospital, the cancer centre, came over to our department and we would have discussions about the best treatments for head and neck cancer patients," says Lefebvre, who became senior resident in the ENT head and neck service at the University Hospital. "It was one of the first collaborations between a cancer centre and a general hospital, and I was fascinated by this multidisciplinary approach involving patients. It was very satisfying."

Unslicing the patient

Joining the Centre Oscar Lambret as a head and neck surgeon in 1976, he discovered the world of the large multidisciplinary team, including surgeons, medical oncologists, radiation therapists, pathologists, biologists and social workers. And when he became deputy director of the centre in 1996 – a post he held for five years – he set about changing the structure of the centre so that the patient became the focal point of this multitude of professionals working together.

At the time, the hospital was organised so that patients worked up the three floors of the hospital – from surgery on the first floor, to medical oncology on the second, to radiation therapy on the third. The management team dismantled the approach, which he says "cut the patient into slices". They reorganised so that the patient stayed in the same department, with different professionals revolving around them. "They can stay with the people they have got to know, and know where they are. It's far more comfortable." It's an approach that is now interesting other hospitals in France.

Already involved in French head and neck study groups, Lefebvre moved into the international cancer scene in the early 1980s. Working as a head and neck specialist at the cancer centre, he was charged with keeping up to date with developments in treatments beyond surgery. He became involved in the main study group on head and neck cancers in Europe at the time, run by the European Organisation for the Research and Treatment of Cancer (EORTC), and was asked to be the chairman in 1989 – a role he continued until 1998.

"I realised there was a need for European collaboration, because I met people with different concepts. Here we were in Latin Europe, where surgery was the main treatment for head and neck cancer. But working with people from Scandinavia, it was clear that radiation and oncology were the main treatments. We had two different philosophies, and we had no idea who was right. So the

AEON VERLAG & STUDIO

Making sense. This play about a hard-bitten gruff man who finally gives in to his daughter's pleas to have a lump in his neck checked out, only to be paralysed by a stream of frightening and unintelligible information from the doctor, aims to raise awareness of the problems many of these patients face

need for collaborative studies was clear." This new international collaboration led to him leading far-reaching developments in the treatment of head and neck cancers of which he remains proud.

The potential of chemotherapy to treat people with advanced head and neck cancers was just beginning to be understood – Lefebvre remembers hearing the "earth changing" results of two studies reported at ASCO in 1982 showing that a new chemotherapy protocol (cisplatin and 5-fluorouracil) produced impressive response rates in previously untreatable cases of head and neck cancer. "This meant that we now had three partners: the surgeon, the medical oncologist and the radiation oncologist, and now we had to integrate chemotherapy in treatment with curative intent. It was a complete change, and the beginning of another aspect of my career."

Pioneering personalisation

Lefebvre, among others, used this knowledge to devise new approaches to identify patients for whom non-surgical treatments would work well. "Those patients who were good responders to chemotherapy were also good responders to radiation. So we said: OK, we can use chemotherapy as a way of selecting two groups of patients – those who are still candidates for total laryngectomy, because they do not respond enough to chemotherapy, and those who are good responders, who can move to irradiation." The result was that total removal of the larynx – and therefore loss of voice and permanent tracheostomy – became no longer necessary for selected patients with advanced cancer.

The work, which he sees as a continuation and logical conclusion of his research into new surgical techniques with Piquet, made him a world authority on larynx surgery, organ preservation and clinical research. He has contributed hundreds of papers, abstracts and chapters, given numerous oral presentations and been invited to lecture throughout the world.

What is ironic, but also indicative of his multidisciplinary outlook, is that he established his authority as a surgeon by promoting non-surgical approaches. "It's not rare at international meetings that I am introduced as a medical oncologist or a radiation oncologist. Some people don't think I'm a surgeon, because I discuss all the disciplines and

"We had no idea who was right.
So the need for collaborative studies was clear."

talk about non-surgical treatment!"

He was appointed director of the International Federation of Head and Neck Oncology Societies in 2002 and then president of the International Academy of Oral Oncology. As his profile rose, and with it interest in all aspects of the treatment of head and neck cancers, he realised there was a need for a truly European body to bring together national expertise. Building on networks of head and neck societies already established in northern Europe, he was one of the founders of the European Head and Neck Society (EHNS), a federation of national societies which began holding regular scientific meetings in 2001 and was officially constituted in 2006. Lefebvre is its first president.

Communicating with patients and the public

It was the EHNS that decided to work with Merck Serono (Lefebvre is a member of its advisory board) on finding out more about why so many cases of head and neck cancer were diagnosed late. The result, in 2008, was the 'About Face' survey of 7000 people in Europe, which found that public awareness of head and neck cancer was extremely poor. As many as 20% of respondents believed head and neck cancer affected fewer than 1000 people in Europe – one hundredth of the correct figure. Over half (including health workers) incorrectly believed head and neck cancer affects the brain.

For Lefebvre, one of the most important findings was that when people did know something about head and neck cancers, it came not from doctors, but friends, relatives and the media. "This shows that clearly we need to work with the media," he says.

A follow-up survey in 2010 included detailed interviews with patients, and confirmed that communications with doctors were very poor. Merck and the EHNS decided that a symposium including a drama at ESMO would be a powerful way of presenting the issues. The symposium drew 40 journalists from different countries, with Lefebvre providing at least ten press interviews. A follow-up meeting in London attracted similar interest. Now EHNS is considering publishing a brochure in very simple language, and in different languages, aimed at general practitioners, dentists and pharmacists.

Lefebvre realises that the reasons for delays in diagnosis are complex and solutions aren't easy to find. Research at the Centre Oscar Lambret indicates that 80% of head and neck patients come from the poorest strata of society, 31% live alone at the time of diagnosis, and only a tiny minority are working. These groups have concerns about entering a healthcare system for financial, personal and cultural reasons. Quite often they genuinely believe their symptoms are nothing to worry about, because they have lived with tobacco-induced throat inflammation for a long time anyway.

But he is convinced that more could be done through publicity campaigns. He believes celebrities and public figures are particularly good at bringing previously taboo subjects like cancer out into the open – particularly in Latin cultures, where he says private concerns such as illness are rarely discussed in public. The honesty of film star Michael Douglas talking about his throat cancer has set a positive example, which he'd like to see followed by other celebrities in Europe.

When it comes to supporting these patients once they are in the health system, there's plenty that health professionals can do. "We have to think about how to organise the process of information-giving from the moment of diagnosis onwards," he says. At the Centre Oscar Lambret patients are first given very basic information about cancer and their diagnosis, and a simple note for them to read about what happens next. This can be discussed with their physician at the next appointment. There is also a consultation with a nurse a couple of weeks after diagnosis. "It's much easier for patients with this social profile to openly discuss with a nurse than a physician, particularly if they have 'Professor' written on their badge!"

Clinicians also need more guidance on head and neck cancers, he believes – both on clinical research

"When people did know something about head and neck cancers, it came from friends, relatives and the media"

"If head and neck surgeons want to continue to be chiefs of the orchestra, they must know every instrument"

in the field, and communication issues. At Lefebvre's suggestion, courses on head and neck cancers run by the radiation-oncology society ESTRO will, from this year, include an hour on clinical research, and next year the course will include an hour with a communication specialist, explaining how to communicate bad news to patients. He has also approached the European School of Oncology about the possibility of including communication training in head and neck courses.

Underlying all Lefebvre says is the unshakeable principle that, for all their difficulties, this group of patients is as worthy of respect and professional effort as any other. "They suffer from stigma, but as soon as they become confident in us here, they accept us and what we have to say totally. It is extremely rare for a patient to refuse to sign a consent form to enter a clinical trial. In my whole professional life I have been insulted just twice."

Now 65, Lefebvre is not facing the prospect of next year's retirement – and separation from these patients – with particular relish, and expresses mild envy at the opportunities and challenges younger generations will face. "Many things are changing. Now every year we have new approaches – minimally invasive surgery, reconstructive surgery, biotherapies, new radiotherapy techniques. Modern functionional imaging and biology is also bringing new diagnostic tools. Now we have to work to validate all the treatments.

"The goal for the new generation is to work together to find an evidence-based approach to the best options for each patient."

"I often say, the gold standard of care does not exist. There is only one standard – the multidisciplinary approach, and the role of the tumour board to select from all the variegated options what is best for the individual patient. And if head and neck surgeons want to continue to be chiefs of the orchestra, they must know every instrument."

Lefebvre has always drawn a strict line between family life and professional life, never mixing the two, protective of his family's privacy. He has three children, and one daughter is an oncologist – but they never talk shop together, not even when both of them are attending the same cancer conferences. Home is home, work is work. But he isn't quite sure what he will do when all his time is home time: maybe he'll take up golf again, travel with his wife, maybe do some more cooking. He will, he observes, have more time for his grandchildren than he has had for his children. But in a year or so he certainly won't be lecturing, or doing anything to suggest that he is still one of the world's leading experts on head and neck cancers. There is an art, he says, to knowing when to leave the stage to others. It will be in good hands.

"You lose your credibility and your contact with the real world when you stop seeing patients on a regular basis," he says. "In ten years, many things will change, and a new generation will do these things better than I."

If you could see it through my eyes...

Why cancer patients can find it hard to stick to their prescriptions, and how to make it easier

➜ Peter McIntyre

Cancer patients who do not share their doctors' belief in the drug they are prescribed, or find living with the side-effects hard to bear, may fail to take their pills according to the prescription – and may prefer to keep this failing to themselves.

Just before Easter, a group of women who had been treated for breast cancer gathered at the Europa Donna House in Cyprus. One of their younger members arrived smiling, carrying a cake and in the mood to party: she had just completed five years of tamoxifen.

Stella Kyriakides, president of the Cyprus Europa Donna Forum recognised the feeling, "For her doctor it may have been a routine daily tablet, but for her it was a symbolic moment when the five years were up – a celebration that she had finished her medication."

Thousands of women and men around Europe no doubt celebrate when they complete a course of cancer treatment without the disease re-emerging. However, thousands of others never complete the treatment – they stop the medication early or miss so many doses they put effectiveness at risk.

The consequences of taking cancer medication irregularly can be severe, even fatal. Cancers may return or doctors may prescribe stronger doses, thinking that the cancer is not responding to treatment. If the drug is part of a clinical trial then lack of adherence can affect the findings. The problem is growing as more and more cancer patients manage their own medication, taken orally as an adjuvant therapy or to keep cancer under control.

Those who have studied issues of adherence suggest that patients are reluctant to tell their doctors when they are missing doses or having trouble with side-effects, while many doctors assume that all their patients are complying 100%.

A NO-BLAME APPROACH

Rob Horne, professor of behavioural medicine at the School of Pharmacy in the University of London, says, "Non-adherence is a problem but it is not the patient's problem. It is really an indication that something has gone wrong in the process of delivering care. We need a 'no-blame' approach."

There are basically two reasons why people don't take medicines, says Horne: they can't or they don't want to. Offering patients simple practical support such as providing clear instructions or issuing reminders is important, he says, but it is not enough. "We also have to consider patients' beliefs about the treatment."

Horne describes the way patients think about their need for medication as "necessity beliefs". These beliefs, and the way patients think about risk of harm, affect their decisions.

"We need to understand that the person is not a blank sheet of paper you can write a prescription on. They come to the consultation with a pre-existing set of beliefs about the illness and treatment, which are often logical even though they may differ from the medical view. Those beliefs will influence the perceived salience of the advice and whether they follow it. That is the message we need to get across."

ILLUSTRATION: FRED VAN DEELEN

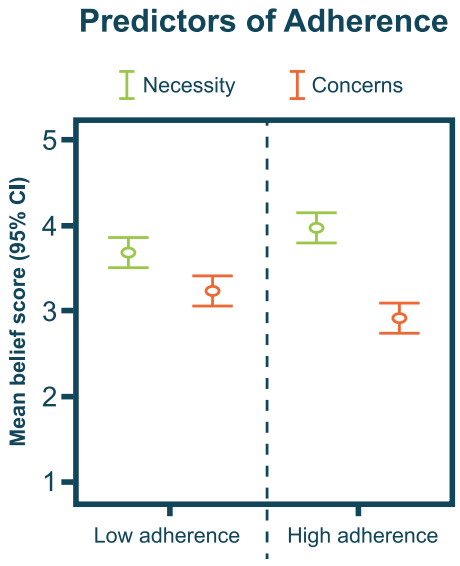
ADHERENCE IS AFFECTED BY CONCERNS AND BELIEFS

Rob Horne, professor of behavioural medicine at the School of Pharmacy in the University of London, has shown in a number of disease settings that people are more likely to adhere to their medication the fewer concerns they have about the negative effects of the medication and the more convinced they are that they need treatment and the medication in question will benefit them.

Responses to a questionnaire about perceptions of anti-retroviral therapy administered to people with HIV before they started treatment revealed a range of concerns:

- 68% worried about the long-term effects of the medications
- 55% worried about unpleasant side-effects
- 50% were concerned that the medicines would disrupt their lives
- 47% were simply worried about having to take the medicines
- 31% worried about having to take the tablets at the same time every day
- 30% worried about becoming too dependent on the drugs
- 21% ticked the box "these medicines are a mystery to me"

When each person's responses were combined to form their mean belief scores in terms of 'concerns' and 'necessity', these were found to clearly correlate with levels of adherence 12 months after the start of their treatment (see figure).



A greater belief in the treatment and fewer concerns about the downsides of the medication were associated with greater adherence to their prescribed drugs in this study of patients living with HIV

Source: R Horne et al. (2007) *JAIDS* 45:334–341

Patients who are well-informed may or may not do what their doctor hopes, but if they discuss with their oncologist and understand the issues, they can make an informed choice. One breast cancer patient might be convinced by their doctor that their risk of becoming depressed on tamoxifen can be managed. Another might fear the bone mineral density loss and joint pain that has been associated with aromatase inhibitors. The important thing is that patients discuss their fears with their physicians.

THE NON-ADHERENCE NON-CONVERSATION

But as Estelle Lecointe, founder of the French patient support group Ensemble contre GIST, explains, patients can find it very hard to discuss non-adherence and doctors are not too good about asking.

In her particular disease, the key drug is imatinib – Glivec – originally approved for use in chronic myeloid leukaemia and later found to be highly effective in a large proportion of GIST patients, who had few other options. Patients can feel guilty and ashamed about failing to take their medicine as prescribed, says Lecointe, which can make it hard even for patient advocates like her to collect testimonies about non-compliance. "These patients generally write privately to me to explain to me the kind of problems that they face. They don't want to speak about this to other patients. It is difficult to address in the family because patients are afraid of disappointing their relatives. It is even more difficult to speak about it with the physicians, because the relationship between the patient and the physician is also a matter of trust."

"I was 33 years old. I wanted to get to know what life without Glivec could be"

Physicians, on the other hand, have been so impressed by the drug, she says, that they didn't even consider the possibility that their patients might not take it. "We also have many physicians who were convinced that their relationship with the patient was so good that they would tell them if they had these kinds of problems. This was also false unfortunately. We have huge work to do in terms of communication and education towards the physicians, even though some of them have started to understand."

Estelle Lecointe

A life without Glivec

Doctors who want to understand why a patient might feel compelled to stop taking a potentially life-saving drug need look no further than Estelle Lecointe herself. Diagnosed with GIST in 2005, she was among the first generation of patients to be treated with Glivec at the Institut Gustave Roussy in Villejuif, Paris. Yet in 2009, after three years in full remission and well aware of the risk she was taking, she decided to come off the drug. "It was a question of psychological survival," she says.

Lecointe had been living with this disease since the age of 19, when it had been diagnosed, incorrectly, as a schwannoma. Ten years later she was told she had a cancer of the stomach lining and after a period of ping-ponging between surgeons who did not know what to do with it, ended up at the Gustave Roussy, where the tumour was recognised as GIST.

She was started on 400 mg/day Glivec, which she found difficult. "I started to take the pill after breakfast but quickly realised I was very tired for the rest of the day. I tried various options and finally decided to take it at dinner, because it allowed me to stay awake at work and sleep better at night." Things became worse when her doctor increased the dose to 600 mg/day, to be taken in two doses, after finding micrometastases in her liver.

"I had ascites [fluid in the peritoneal cavity] and a lot of diarrhoea. These side-effects made my life difficult on a daily basis, but it was worth taking it because my micrometastases apparently disappeared and made the surgery feasible."

After undergoing an operation to remove four metastases from her liver, she went through a difficult recovery, and then she restarted Glivec, which she took for the next three years. It was at this point, still in complete remission, that she decided she needed a break.

"It was not an easy decision to make but I was very tired with this. I had gone through very hard times with the surgery, and I was 33 years old. I wanted to get to know what life without Glivec could be, even though it might last only one or two or maybe six months."

Having been diagnosed at such a young age, she feels, makes it harder to live with psychologically. "It is quite hard to project yourself forward because it means that you remain a cancer patient for the rest of your life."

Because she had been in full remission for three years, Lecointe's oncologist accepted her decision on condition that she committed herself to restart Glivec if she relapsed. Three years on, she is still off the drug and in remission. "It is a miracle," she says, "but I have to keep in mind that one day or another it will be back, because I have already relapsed twice in the past. But it was important for me to be able to live

for even a short period of time without treatment."

Lecointe believes that any patient can have adherence problems if the therapy becomes an obstacle to their hopes. "For example, when you start Glivec you are told that you will not be able to bear children. Because you are scared of the idea of dying you accept it. Then maybe three or four years later someone realises that she will spend her life taking this treatment and will not be able to raise her own family. I talk to a lot of women of my age who consider stopping imatinib to get pregnant without telling their doctors. It is one of the most frequent reasons young adults give for stopping."

I'm 99% adherent

Giora Sharf, a CML patient advocate, recognises the particular problems faced by younger patients from his own experience running the Israeli Patients CML Group. His group recently held a large meeting with a doctor from Germany, and a few young patients turned up. "Most of the questions from them were: 'Can I stop taking the drug?'"

Giora Sharf

Sharf himself, however, feels much more relaxed about his daily dose of Glivec, and describes himself as 99% compliant. His cancer story started 12 years ago when he was told he had only three years to live. He found his way on to the first Glivec trial through searching the internet, and was highly motivated to use the medication as prescribed.

After two years he achieved complete molecular response. "My doctor could not tell me whether I was cured or not. I was his first patient whose condition was undetectable and he could not tell me if there was still disease in my body."

It was what he did next, though, that may have played an important role in shaping what Horne describes as his "necessity beliefs". Sharf and his doctor implemented a very careful stopping trial, with close monitoring of the disease, to find out what would happen. "After two months my disease started to relapse, so I knew that I was not cured; I needed to continue to take my Glivec."

Sharf believes there hasn't been one day when he did not intend to take the medication, though like other people he may forget once in a while. "I don't worry about it too much. I know from all the research that if you take more than 90% of the medication you are supposed to take, you are in a good situation. I do my PCR test every six months and I have been completely negative for more than eight years."

Forgetfulness and side-effects are two reasons why patients miss doses, says Sharf. "Side-effects are something that you cannot avoid, but most of them are something that you can learn to live with. For me personally it is not that terrible. I suffer from fluid retention; I wake up every day and my eyes are swollen. I look a little bit like a zombie. It gets a little bit better during the day. Often in the middle of the night you jump out of bed with muscle cramps in your leg. You get tired more quickly than other people. Sometimes I complain that I might be suffering from memory impairment, but everyone tells me it happens when you are 60 years old!"

Not everyone is so lucky, he acknowledges. "Some people have a terrible rash all over the body and they are scratching and itching. Others have bone pain and vomiting and diarrhoea."

It's understandable, then, that some people want to take a 'drug holiday'. "Someone is going on

"Most of the questions from the younger patients were: 'Can I stop taking the drug?'"

"Rarely do oncologists ask if you are missing doses, or they ask in such a way that you will not admit to it"

vacation. He says, 'OK I feel good, my results are good why can't I stop for a few days, two weeks and feel like I did before I got sick?'"

Some place their lives in the hands of fate or their god. "In Israel, there are very, very religious orthodox people. In my group there are a few of them who just said I will stop taking the drug and whatever God wants to happen will happen. Of course, we have lost a couple of them to the disease."

For others, non-adherence is about following their own logical (if not evidence-based) beliefs. "I have a good friend from the US who is a doctor himself, and he believed that stopping every few months for two weeks could improve the outcome. He had a theory that when you stop, the blood cells are going to start multiplying and then it is going to be easier for Glivec to destroy them. Of course it did not work and once his disease started to relapse, he started to have to take his drug on a daily basis again."

It's the price you pay

Adherence is also becoming recognised as a major issue for a much larger group of patients – namely those with breast cancer – due to the steady increase in oral drugs over the past 20 years. So says Stella Kyriakides, who in addition to her position as president of Europa Donna Cyprus, is a member of parliament and, until June 2012, chair of the Patients' Advisory Committee for the European Cancer Organisation (ECCO).

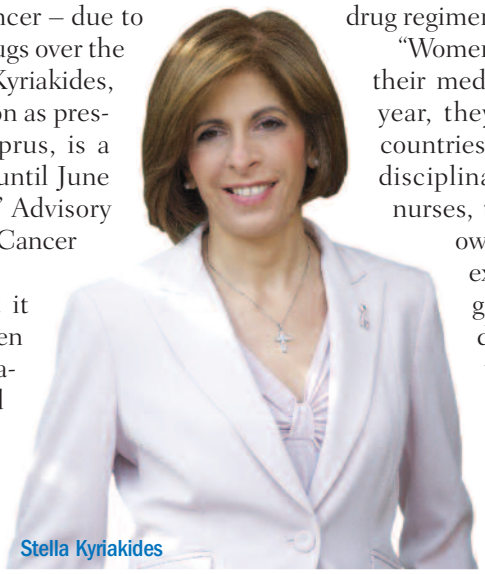
"Initially it was felt that it was almost obvious that women would adhere to their medication. As time has gone on, and more and more oral anti-cancer drugs are being used and in the metastatic settings, what seemed obvious is not so obvious. First of all, side-effects have been widely understated, leading to many women not adhering to their medication.

"In the case of early breast cancer, you are asking women who have had surgery and radiotherapy and who are, to all intents and purposes, free of the disease, to take a medication which may impact on their quality of life, not to address a disease, but a risk of recurrence. It is quite different to women taking drugs for treatment in a metastatic setting."

Kyriakides is herself on her eighth year on a daily dose of letrozole (Femara), an aromatase inhibitor. Despite joint pain, Kyriakides has learnt to cope with side-effects. "You take some Panadol or something if you are having a bad time with it, and you get on with your life. I tell women the side-effects are there and it is the price you pay. If you believe in what you are taking then you tend to adhere. But I am very involved in advocacy and not a typical case."

Kyriakides believes that the problem of non-adherence is largely hidden, and says Cyprus Europa Donna is planning its own survey to see how women on oral therapy manage their drug regimens.

"Women are treated and then given their medications and, after the first year, they are seen six monthly. In countries where there are no multi-disciplinary teams and no breast nurses, they are rather left on their own," she says. "From personal experience, rarely do oncologists ask if you are missing doses, or they ask in such a way that you will not admit to skipping doses or forgetting. This lack of open communication between patients and doctors about lack of adherence has to be put on the table."



Stella Kyriakides

"If non-adherence is not addressed there could be a backlash"

Tackling the adherence problem

There are many suggestions for improvements that would help cancer patients to adhere more closely to their prescribed doses. However, even obvious-sounding solutions can run into trouble. The pilot survey of CML patients found that 88% of patients who admitted to missing doses said they simply forgot. But when it was suggested that they use reminders, ranging from fridge magnets to daily phone alarms, 80–90% of patients said they did not want them. Giora Sharf says that forgetfulness often goes deeper. "Psychologically, they don't like to be patients and don't want to be reminded on a daily basis that they are sick."

He is now working with the CML Advocates Network – which covers 68 CML patient groups from 52 countries – on an internet survey of patients in 12 languages, hoping for 2000 responses. This will be run in conjunction with doctors' CML groups in France and Italy, where patients will also be offered a paper-based questionnaire, to check against bias in internet-only surveys. "The main goal is to try to develop tools for patients and for doctors and nurses which will start to improve adherence to the drug," he says.

Kyriakides agrees that it is important to look into why someone is missing doses. "Women may not be adhering because of personal characteristics, because of treatment features or because of other features that have to do with the way that medical care is provided. Do they have to get the prescription from the hospital and then go to another place to have it filled? I think there are a lot of issues that need to be addressed." She would also like to see better packaging. "If you are taking a pill every day and the packaging does not have any day or date, it is very easy, although it sounds really silly, to think you have taken it and then not be sure. And you are told you should never double dose." Both Sharf and Kyriakides believe that supportive families make a big difference in creating a positive routine for taking medicines.

Rob Horne has devised two short questionnaires. One looks at how far people adhere to their medication, and by offering a range of choices, gives them 'permission' to admit to skipping doses. The other looks at patient beliefs about the necessity for the medication and concerns about long term use. The example Horne often gives is of people with asthma who are on long-term preventive medication, but believe they should only take it after an attack. In the case of cancer too, many patients do not understand the risks.

"We somehow need to understand or to recognise the uncertainty and look at how we communicate and negotiate that. Most clinicians think they haven't any time, but that is part of the challenge. There are ways that one can build programmes that actually help to do this in practice."

The stakes are high and as the number of expensive oral therapies multiplies, getting higher. As Kyriakides notes, "Science has moved on. The industry and oncologists have provided us with the tools to realistically prevent and in some ways cure breast cancer and to have women living with metastatic disease with a very good quality of life. But we have really not addressed the issue that, for many different reasons, women may not be adhering to their orally administered targeted therapies."

Rob Horne fears that if non-adherence is not addressed there could be a backlash. "We have to be careful that we study patient perspectives properly in cancer so we can offset any reaction along the lines of, 'These drugs are really expensive. Why are we bothering to prescribe them if half the patients don't take them?'" The true cost, he says, is to the health of the patient whose condition is under-treated. "We need to support patients to make informed choices about treatment and get the best from prescribed medicines."

IMPACTFACTOR

nature REVIEWS CLINICAL ONCOLOGY

Salvage chemotherapy in gastric cancer – more than a straw?

Florian Lordick

The benefit of salvage chemotherapy in gastric cancer refractory to first-line platinum and fluoropyrimidine therapy was previously unknown. A randomised multicentre study has shown that irinotecan or docetaxel administered as single agents improved survival compared with best supportive care alone. Hence, salvage chemotherapy is now a proven option in pretreated gastric cancer.

This article was first published online in ***Nature Reviews Clinical Oncology*** on 1 May 2012, and is republished with permission. doi:10.1038/nrclinonc.2012.76

Gastric cancer is one of the most common and fatal malignancies. Despite a decreasing incidence in Western civilisations,[1] gastric cancer accounts for approximately 700,000 deaths every year worldwide.[2] Cure can only be achieved in the early stages, and the treatment of metastatic disease pursues only palliative goals. First-line chemotherapy with platinum compounds and fluoropyrimidines had a proven role in prolonging survival and controlling disease-related symptoms in advanced stages,[3] but the role and benefit of second-line or further-line chemotherapy was undefined.

Now, a prospective randomised multicentre study called 'salvage chemotherapy', conducted by Korean investigators, has unravelled the value of further-line chemotherapy following failure of first-line or second-line chemotherapy.[4] Kang and colleagues selected patients with advanced-stage gastric cancer who had not responded to one or two prior chemotherapy regimens involving both fluoropyrimidines and platinum. Eastern Cooperative Oncology Group performance status was 0 or 1. Patients were randomly assigned in a ratio of 2:1 to receive salvage chemotherapy plus best supportive care or best supportive care alone. Choice of salvage chemotherapy – either docetaxel 60 mg/m^2 every three weeks or irinotecan 150 mg/m^2 every two weeks – was left to the discretion of the investigators. The primary endpoint was overall survival. Median overall survival was 5.3 months among the 133 patients in the chemotherapy arm and 3.8 months among the 69 patients in the best supportive care arm (HR=0.657, 95%CI 0.485–0.891; one-sided P=0.007). Overall survival benefit for salvage chemotherapy was consistent in most of the prospectively defined subgroups, which included age, performance status, number of prior treatments, metastatic sites, haemoglobin levels, and response to prior chemotherapy. Salvage chemotherapy was generally well tolerated, and adverse events were similar in both arms. No difference in overall survival was found

between docetaxel and irinotecan (5.2 months vs 6.5 months; P=0.116). In summary, the study by Kang and colleagues[4] proves the value of salvage chemotherapy in pretreated advanced-stage gastric cancer. Single-agent chemotherapy improves survival when added to best supportive care and, as single agents, irinotecan and docetaxel are equivalent options.

Both regimens showed good safety profiles, manageable toxicity and good feasibility. Although haematological toxicities were more common in patients treated with chemotherapy, non-haematological adverse events were seen in both arms, indicating that symptoms may have been disease related, rather than treatment related.

The investigators should be commended for the conduct of this informative trial. Do the results come as a surprise and will they alter our daily clinical practice? I feel that both questions can be negated. The results match our expectations and, as clinical oncologists, we have been using second-line chemotherapy for advanced-stage gastric cancer for quite a while.

Experiences from East Asia suggested a clear benefit of sequential treatment for advanced-stage gastric cancer.[5] Relatively long intervals have been reported between the failure of first-line chemotherapy and death in studies in which consecutive lines of chemotherapy were administered in the majority of patients. For example, in a Japanese study that compared the drug S-1 administered as first-line alone or in combination with cisplatin, 75% of patients received post-progression chemotherapy. This treatment administered on disease progression consisted mainly of taxane-based (or irinotecan-based) regimens. Progression-free survival of first-line treatment was four months and six months, respectively, whereas survival following first progression was seven months in both arms.[5] It must be assumed that a much shorter post-progression survival would have been observed if less 'salvage chemotherapy' had been given in the post-progression phase of this study.

Despite the progress in the treatment of advanced-stage gastric cancer that has been observed by the Korean investigators, we must not overlook the purely palliative character of any chemotherapy in this disease. For me, the term 'salvage chemotherapy' is unfortunate. The word 'salvage' is based on the Latin word 'salvare', which means that someone can be rescued and that lives can be saved. But, what is more inapplicable to chemotherapy-refractory advanced-stage gastric cancer than the promise of rescue and cure by offering further chemotherapy? The metaphor that would come closer to the reality is the drowning man who will clutch at a straw. We must not forget that the battle of patients with chemotherapy-refractory advanced-stage gastric cancer is inevitably lost and death will usually arrive at short term. The chance of inducing a new 'response' – whatever that means for the prognosis – is no more than 10% according to the Korean data.[4] The realistic achievements of second-line irinotecan or docetaxel are a transient deferral in tumour progression, a moderate prolongation of the remaining survival time and, possibly, a better control of disease-related symptoms (which has not been assessed in the Korean study). We must learn to talk honestly with our patients. We must be aware that the early communication of the palliative nature of all treatment efforts is beneficial if, in addition, we also support patients in making their decisions and finding their way not out but through the disaster of suffering from a malicious disease and facing death. Jennifer S. Temel and colleagues recently demonstrated that an early palliative intervention following new diagnosis of metastatic non-small-cell lung cancer – a disease with many similarities to gastric cancer – led to improved survival, better quality of life, improved mood and less use of chemotherapy in the last two months of lifetime compared with patients who received standard care.[6] This is not meant as a plea against second-, and further-, line chemotherapy in advanced-stage gastric cancer. Rather, I clearly vote for a frank communication with our patients about realistic treatment goals, for shared and informed decision making, and for palliative support that goes beyond second-line chemotherapy and standard (undefined) best supportive care.

Is irinotecan or docetaxel the only medical option that there is for treating post-progression gastric cancer?

> **"The metaphor that would come closer to the reality is the drowning man who will clutch at a straw"**

Key points

- Second-line chemotherapy improves outcome in advanced-stage gastric cancer
- Irinotecan or docetaxel administered as single agents are proven options in pretreated gastric cancer

Certainly not; more potentially active drugs are available, including other taxanes and alternative platinum compounds that are probably not completely cross-resistant to cisplatin, which is most commonly used in the first-line setting. Even anthracyclines or mitomycin may show benefit in further treatment lines. To date, single-agent irinotecan, given in a biweekly (150 mg/m²) or three-weekly (250–350 mg/m²) schedule has the best evidence to improve survival and symptom control in post-progression advanced-stage gastric cancer. A smaller randomised German study of the Arbeitsgemeinschaft Internistische Onkologie (AIO) showed a consistent benefit for second-line treatment with irinotecan that resulted in a reduction of the hazard ratio for death to 0.48 (95%CI 0.25–0.92, *P*=0.012) in the irinotecan arm compared with best supportive care alone.[7] Beyond chemotherapy, medicinal pain management, nutritional support, psycho-social support and many other interventions do not yet have proven benefit for patients with advanced gastric cancer.[3]

A consistent benefit of 'salvage chemotherapy' has been observed in most of the prospectively defined subgroups of the Korean study.[4] Nevertheless, in the era of personalised medicine and increasing disease stratification, the benefit of specific medicinal interventions must be challenged in future studies that may assess whether this benefit might be the same for different ethnic subgroups,[8] for different histological phenotypes,[9] and for different gastric cancer genotypes.[10]

In summary, irinotecan or docetaxel significantly prolonged overall survival compared to best supportive care in the studied patients. Second-line chemotherapy can now be considered as a proven treatment option for pretreated advanced-stage gastric cancer and this option should be integrated into a comprehensive palliative care strategy.

References

1. R Siegel, D Naishadham and A Jemal. (2012) Cancer statistics. *CA Cancer J Clin* 62:10–29
2. F Kamangar, GM Dores and WF Anderson. (2006) Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *JCO* 24:2137–50
3. AD Wagner et al. (2006) Chemotherapy in advanced gastric cancer: a systematic review and meta-analysis based on aggregate data. *JCO* 24:2903–09
4. JH Kang et al. (2012) Salvage chemotherapy for pretreated gastric cancer: a randomized phase III trial comparing chemotherapy plus best supportive care with best supportive care alone. *JCO* 30:1513–18
5. W Koizumi et al. (2008) S.-1 plus cisplatin versus S.-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 3:215–221
6. JS Temel et al. (2010) Early palliative care for patients with metastatic non-small-cell lung cancer. *NEJM* 363:733–742
7. PC Thuss-Patience et al. (2011) Survival advantage for irinotecan versus best supportive care as second-line chemotherapy in gastric cancer – a randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). *Eur J Cancer* 47:2306–14
8. VE Strong et al. (2010) Comparison of gastric cancer survival following R0 resection in the United States and Korea using an internationally validated nomogram. *Ann Surg* 251:640–646
9. M Messager. (2011) FREGAT working group – FRENCH. The impact of perioperative chemotherapy on survival in patients with gastric signet ring cell adenocarcinoma: a multicenter comparative study. *Ann Surg* 254:684–693
10. IB Tan et al. (2011) Intrinsic subtypes of gastric cancer, based on gene expression pattern, predict survival and respond differently to chemotherapy. *Gastroenterology* 141:476–485

Author affiliations

Klinikum Braunschweig, Department of Haematology and Oncology, Braunschweig, Germany

Competing interests

Florian Lordick declares associations with the following companies: Pfizer, Sanofi-Aventis

Manufacturer sponsorship bias in economic analyses matters

➜ David Kerr and Ahmed Elzawawy

A qualitative study indicates that there is a positive selection bias towards favourable economic analysis of targeted therapies when these are funded by the manufacturer. At a time of increasing budgetary constraints and public scrutiny of the relationship between industry and the professions, we need a more mixed economy of funding for this field.

This article was first published online in ***Nature Reviews Clinical Oncology*** on 1 May 2012, and is republished with permission. doi:10.1038/nrclinonc.2012.75

In terms of the history of medicine and health care, the 19th century may be regarded as the century of Public Health, clean water, sewerage and understanding the basis of infection; the 20th century might be regarded as the century of knowledge, when systematic clinical and laboratory research yielded extraordinary insights into the mechanism of disease; we predict that the 21st century will be driven by value. Considering the spiralling costs of healthcare and an often confused approach to how we define value in a societal

sense, and given the global financial crisis and the likelihood that for many nations the health budget will flatline, it is obvious that we need more data on the relative cost-effectiveness of innovative diagnostic or therapeutic agents if we are to make transparent and defensible judgements on their relative worth. This situation is set against a backdrop of increasing suspicion from policy and lawmakers and some patient groups that the relationship between practising clinicians and purveyors of these new technologies is not at sufficient arm's length.[1] In 2007, Djulbegovic et al.,[2] published a fascinating historical case study of the first conflicts of interest policy at the National Academy of Sciences. A fundamental debate in this case was whether one can simply declare a financial interest or whether one must also admit that this financial interest is a potential source of bias.

Now, a new study has been published by Valachis et al.[3] that addresses this question in a different way. One of the characteristic points of the study is that the authors tried to investigate the role of manufacturers' influence in various manifestations, such as the presence of any author affiliated with the manufacturer of the drug being assessed, or the presence of direct funding from the manufacturer for the health-economic study – as shown in previous studies – the role of funding and its bias in economic evaluation of drugs in oncology,[4] and medical research in general.[5] Of the 81 eligible studies that they identified, the authors found that economic analyses that were funded by pharmaceutical companies were more likely to report favourable qualitative cost estimates than those without an expressed funding association with these companies (28 out of 34 studies [82%] versus 21 of out of 47 studies [45%]; P=0.003). This phenomenon was seen to a similar degree for those studies that reported any financial relationship with the manufacturers, for example, author affiliation or author funding. Valachis et al.[3] discuss the weaknesses inherent in their study with candour: the linkage between the eligible studies and their financial aspects depended solely on published details, as Valachis et al.[3] made no effort to contact authors directly to further verify these data; there may have been a publication bias towards positive reports that might have skewed results; certain study criteria were poorly represented, so the database was rather small (for example, affiliation with manufacturers); and finally, their analysis was based on qualitative data. Nevertheless, Valachis et al.[3] do seem to have demonstrated a consistent sponsorship bias towards the manufacturer of costly, targeted drugs with respect to economic analyses. It is concluded that the best way of dealing with perceptions of sponsorship bias is not increased rhetoric, but rather increased public funding for economic evaluation of medicines, thereby creating a true mixed economy for research funding in this field.

"The way to deal with perceptions of sponsorship bias is not increased rhetoric, but increased public funding"

Does this sponsorship bias matter? If we are to adopt Michael Porter's definition of value,[6] then, yes it does.

"Value in any field must be defined around the customer, not the supplier. Value must also be measured by outputs, not inputs. Hence it is patient health results that matter, not the volume of services delivered. But all outcomes are achieved at some cost. Therefore, the proper objective is ... patient health outcomes relative to the total cost (inputs). Efficiency, as well as other objectives such as safety, is subsumed in the concept of value."

Adoption of any new therapeutic agent in the current climate is likely to involve trade offs, comparing the value gained from the introduction of the targeted therapy relative to existing gold standards in cancer treatment, or, even more widely, comparing its value with that gained from hip replacements or cataract operations. The latter comparison might seem absurd, but within a finite health budget in which there is no ring-fencing of cancer funding, this could become an issue. So an economic evaluation of the new drug will have an often critical role in whether the drug is made available to cancer patients by governments or payers.[7] If there are significant doubts about the veracity of the data, hanging over the analysis like the sword of Damocles, then this starts to undermine the validity of the data and even reduce the chances of a targeted therapy passing over whatever health-economic hurdles have been erected in its way.

So, is there a way to square this circle? In the same way that we now have mandatory listing of clinical trials[8] to offset publication bias, one might establish a register of pharmacoeconomic studies; approaches might be made to journal editorial boards to lower their threshold for publishing negative studies; and

payers could establish independently funded analytical units to give an entirely unbiased view of the economic case for acceptance or not of the agent under investigation. If the workings of these analytical units were utterly transparent and open to public review, then this would further enhance their credibility and relevance to citizens. Do we think that there is some methodical misrepresentation of results? Of course not; however, the paper by Valachis et al.[3] is a timely warning of the subtle biases that can creep in unnoticed, and is perhaps doubly important given the wider economic challenges faced by all healthcare systems and, therefore, the increasing scrutiny that will be applied to all such economic analyses.

References

1. EG Campbell et al. (2007) A national survey of physician–industry relationships. *NEJM* 356:1742–50
2. B Djulbegovic, C Angelotta, KE Knox et al. (2007) The sound and the fury: financial conflicts of interest in oncology. *JCO* 25:3567–69
3. A Valachis, NP Polyzos, A, Nearchou et al. (2012) Financial relationships in economic analyses of targeted therapies in oncology. *JCO* 30:1316–20
4. S Jang, YK Chae, T Haddad et al. (2010) Conflict of interest in economic analyses of aromatase inhibitors in breast cancer: a systematic review. *Breast Cancer Res Treat* 121:273–279
5. M Barbieri, MF Drummond. (2010) Conflict of interest in industry-sponsored economic evaluations: real or imagined? *Curr Oncol Rep* 3:410–413
6. ME Porter. (2007) Defining and introducing value in health care. In: MB McClellan, JM McGinnis, EG Nabel et al (eds). Evidence-based medicine and the changing nature of health care: 2007 *Institute of Medicine (IOM) annual meeting summary,* 1st edn. National Academies Press, Washington DC, chapter 14, pp 161–171
7. R Sullivan et al. (2011) Delivering affordable cancer care in high-income countries. *Lancet Oncol* 12:933–980
8. US National Library of Medicine. (2012) http://www.clinicaltrials.gov

Author affiliations

David Kerr, Nuffield Department of Clinical and Laboratory Sciences, University of Oxford, UK; Ahmed Elzawawy, Suez Canal University, Port Said, Egypt

NEWSROUND

Selected reports edited by Janet Fricker

Stereotactic body radiation therapy for spinal metastases

➜ Lancet Oncology

Stereotactic body radiation therapy (SBRT) delivers significant reductions in patient-reported pain and other symptoms six months post treatment, a phase I/II US trial has found.

Around 40% of cancer patients develop spinal metastases during the course of their disease, inadequate treatment of which results in pain and neurological complications that increase symptom burden and diminish health-related quality of life. SBRT is an emerging technique that uses image guidance to deliver high-dose radiation precisely, creating steep dose gradients at the interface between the spinal cord and tumours. Although SBRT has become an established technique for the management of spinal metastases in recent years, its effectiveness in controlling the symptom burden has not been well described. In 2002, when the current study was initiated, the literature for SBRT was still in its infancy.

In a preliminary report of a prospective phase I/II trial of SBRT, Xin Shelley Wang and colleagues, from the MD Anderson Cancer Center, Texas, detailed the safety, efficacy and patterns of failure for a subset of 63 patients who were followed for up to 50 months. In the current publication, the same team investigate the symptom reduction benefit of spinal SBRT for the whole cohort of patients during the first six months following treatment, and the clinical benefit for up to two years.

Altogether 149 patients with 166 spinal metastases at the cervical, thoracic or lumbar vertebral levels, receiving a total dose of 27–30 Gy, typically in three fractions, were included in the analysis.

Results show that the number of patients reporting no pain from bone metastases (as measured by the Brief Pain Inventory) increased from 26% before SBRT to 54% six months after SBRT ($P<0.0001$). These improvements were accompanied by significant reductions in opioid use – 28.9% of patients used opioids at baseline versus 20% at six months ($P=0.011$).

Furthermore, patients reported significant pain reduction according to the MD Anderson Symptom Inventory (MDASI) during the first six months after SBRT ($P=0.00003$), and significant reductions in a composite score of the six MDASI symptom interference with daily life items ($P=0.0066$).

"This trial provides prospective data that support the careful use of spinal SBRT in selected patients, since SBRT safely and reliably halts the progression of disease while reducing patient symptoms and improving functioning in daily life, as measured by validated methods," write the authors. The study, they add, also highlights the importance of integrating patient-reported symptom assessments with clinical outcome evaluations to fully demonstrate the benefit of SBRT in patients with metastatic spinal disease.

One limitation of this study, they say, is the absence of a control group against which to measure the effect of SBRT on symptom development.

■ XS Wang, LD Rhines, AS Shiu et al. Stereotactic body radiation therapy for management of spinal metastases in patients without spinal cord compression: a phase 1–2 trial. *Lancet Oncol* April 2012, 13:395–402

CMF treatment linked to long-term cognitive decline

➜ Journal of Clinical Oncology

Survivors of breast cancer treated with adjuvant cyclophosphamide, methotrexate and fluorouracil (CMF) chemotherapy scored lower on neuropsychological tests 20 years after treatment

than women who had never had cancer, a Dutch case-cohort study has found, in what is believed to be the longest follow-up ever done of the effects of adjuvant CMF on cognitive function.

Many studies have shown that chemotherapy can induce cognitive changes up to five years following treatment, with differences observed in the domains of memory, processing speed and executive function. But whether chemotherapy has any long-term effects on cognition has been largely unknown.

In the current study Sanne Schagen and colleagues, from the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital in Amsterdam, compared the cognitive performance of 196 patients with breast cancer who had a history of adjuvant CMF chemotherapy (six cycles, average time since treatment 21 years) to that of a reference group of 1509 controls selected from an ongoing population study in the Netherlands who had never been diagnosed with cancer. Women in the study were aged between 50 and 80 years.

Altogether seven neuropsychological tests were administered, which yielded 17 outcomes in the cognitive domains of processing speed, verbal learning, memory, inhibition and word fluency as elements of executive functioning, visuospatial ability and psychomotor speed. Additionally, subjects completed the Mini-Mental State Examination (MMSE) as a screener for dementia.

Results show that the women exposed to CMF chemotherapy performed significantly worse than the reference group in cognitive tests of immediate verbal memory (P=0.015), delayed verbal memory (P=0.002), processing speed (P<0.001), executive functioning (P=0.013), and psychomotor speed (P=0.001). However, women who had undergone chemotherapy were also found to experience significantly fewer symptoms of depression (P<0.001).

"In conclusion, the cognitive functioning of survivors of breast cancer on average 21 years after adjuvant CMF chemotherapy is worse than that of women from the general population who have never been diagnosed with cancer. These data suggest that cognitive deficits following breast cancer diagnosis and subsequent CMF chemotherapy are at least partially long lasting," write the authors.

The results, they add, are highly relevant since the number of long-term survivors of breast cancer is increasing due to improvements in recognition of early-stage breast cancer, ageing of the population, and improved survival after breast cancer diagnosis.

Although information on hormone replacement therapy was not available, the authors did not believe this influenced their findings, since use of such treatments in the Netherlands was low in the years studied.

An important question, say the authors, is the extent to which the observations extend to other chemotherapy regimens, since the CMF regimen is no longer the optimal adjuvant chemotherapy for early-stage breast cancer. "Further studies into the late effects of adjuvant chemotherapy for cancer are needed to corroborate these results and to gain further insight into the mechanisms underlying these observations," they write.

■ V Koppelmans, M Breteler, W Boogerd et al. Neuropsychological performance in survivors of breast cancer more than 20 years after adjuvant chemotherapy. *JCO* 1 April 2012, 30:1080–86

Regional treatments for liver metastases in colorectal cancer

➜ British Journal of Cancer

Transarterial-chemoembolisation (TACE) of patients with unresectable liver metastases from colorectal cancer offers adequate downsizing to allow further treatment with laser-induced interstitial thermotherapy (LITT), a German cohort study has found.

In CRC the hepatic tumour load is an important prognostic indicator for survival, since liver involvement is life limiting. The only curative therapy at the moment is surgical resection, which is not possible for around 75% of patients due to advanced disease or secondary disorders. Regional treatments offer a promising alternative to terminate growth of metastases and extend patient survival.

In the current study, Thomas Vogl and colleagues from Johann Wolfgang Goethe University in Frankfurt, Germany, evaluated a treatment protocol using repeated TACE downsizing with different chemotherapeutic combinations prior to MR-guided LITT in patients with unresectable liver metastases from colorectal cancer.

By embolising the hepatic artery, the authors explain, blood flow is reduced, leading to ischaemia, which increases the contact time between the tumour cells and chemotherapeutic agents. Furthermore the thermal anticancer effect increases with the removal of the cooling effect of the blood flow, which can result in a conservation of viable cells around larger vessels due to a local under-heating. "Hence, TACE combined with MR-guided LITT ablation increases the effectiveness of each of the treatments alone," write the authors.

Between January 1999 and September 2008, 224 patients with liver metastases from CRC underwent 757 TACE sessions (mean 3.4 sessions per patient), and were treated with 492 LITT sessions (mean 2.2 sessions per patient) for post-TACE remaining lesions. The intra-arterial protocol consisted of either irinotecan or mitomycin (n=77), gemcitabine and mitomycin (n=49) or mitomycin alone (n=98) in addition to Lipiodol and Embocept.

Results show that, overall, TACE resulted in a mean reduction in diameter of the target lesions of 21.4%, with a median time to progression of 8 months (calculated from the start of therapy) and a median local tumour control rate of 7.5 months (calculated from therapy completion). The median survival of patients calculated from the beginning of TACE for those treated with irinotecan and mitomycin was 23 months; for those treated with gemcitabine and mitomycin it was 23 months; and for those treated with mitomycin only it was 24 months, with a statistically significant difference between the groups (P=0.01).

After LITT the rate of clinically relevant

complications requiring further interventions was 0.8% (*n*=4); with the most common minor complications being reactive pleural effusions (27.4%, *n*=135), which were self-limiting.

"The large cohort presented in this study confirms that the combination of TACE and MR-guided LITT is a safe and effective treatment for liver metastases of CRC origin," conclude the authors. The combination of TACE and LITT, they add, is a good therapy option for patients not responding to systemic chemotherapy, and also as an alternative to surgery when liver resection is contraindicated. The promising results of the current study should be further evaluated and confirmed in a randomised study, they suggest.

■ TJ Vogl, A Jost, NA Nour-Eldin et al. Repeated transarterial chemoembolisation using different chemotherapeutic drug combinations followed by MR-guided laser-induced thermotherapy in patients with liver metastases of colorectal carcinoma. *Br J Cancer* 27 March 2012, 106:1274–79

PCR test for early lung cancer

→ The Lancet

A quantitative-PCR-based assay for patients with early-stage, non-squamous, non-small-cell lung cancer (NSCLC) reliably identifies patients at high risk of dying after resection. The assay was independently validated in both a large community-based American cohort and a separate Chinese population.

Outcomes after NSCLC resection are poor, with 35–50% of patients suffering recurrence. A more precise staging test would enable clinicians to identify patients with adverse outcomes who would most benefit from adjuvant treatment.

Several groups have developed gene expression analyses that successfully predicted higher than expected mortality after resection of NSCLC, but many of these gene signatures have been based on microarray platforms that need "snap-frozen tissue samples", which are difficult to use in practical clinical settings.

In the current study, Johannes Kratz and colleagues, from the University of California San Francisco (UCSF), developed a 14-gene mRNA expression assay (including 11 target genes linked to the cancer biology and three reference genes used to standardise measurement of the cancer genes) for prognosis in early-stage NSCLC. The assay uses quantitative PCR and runs on widely available formalin-fixed paraffin-embedded tissue samples, whose collection and processing techniques are common in clinical practice.

The investigators first measured levels of the genes in tissue samples taken from 361 patients at UCSF who had surgery for NSCLC. An algorithm then correlated the levels of the 14 genes with the clinical outcomes of the patients, identifying the molecular profiles that were associated with low, intermediate or high risk of death.

Next, the UCSF team blindly examined lung samples taken from 433 other patients with early-stage NSCLC from Northern California, and then used a similar blinded approach to test the algorithm using tissue samples from 1005 lung cancer patients from China.

Kaplan-Meier analysis of the Californian validation cohort showed five-year overall survival of 71.4% of patients judged at low risk, 58.3% at intermediate risk, and 49.2% at high risk (*P* trend=0.0003).

Similar analysis of the Chinese cohort indicated a five-year overall survival of 74.1% at low risk, 57.4% at intermediate risk, and 44·6% at high risk (*P* trend<0.0001)

"Our practical, quantitative-PCR-based assay reliably identified patients with early-stage non-squamous NSCLC at high risk for mortality after surgical resection, discriminating such patients with greater accuracy than use of NCCN criteria alone," write the authors.

The study, they add, represents the first of its kind involving the extraction of interpretable RNA from formalin-fixed paraffin-embedded tissue. Additional strengths include the performance of the assay in an independent laboratory and the use of a second cohort with a different genetic background.

In an accompanying commentary, Yang Xie and John Minna, from the University of Texas, Southwestern Medical Center, say that it will be important to determine whether the assay works in squamous-cell lung cancer and all NSCLCs, irrespective of their histological subtype. "If not, other signatures will need to be developed," they write.

■ J Kratz, J He, S Van Den Eeden et al. A practical molecular assay to predict survival in resected non-squamous, non-small-cell lung cancer: development and international validation studies. *Lancet* 3 March 2012, 379:823–832

■ Y Xie, JD Minna. A lung cancer molecular prognostic test ready for prime time [commentary]. *ibid* pp 785–787

Metformin shows survival benefit in pancreatic cancer

→ Clinical Cancer Research

Patients with diabetes and pancreatic cancer who are prescribed the anti-diabetic agent metformin showed improved survival in comparison to those who did not receive the drug, a retrospective US study has found.

Diabetes and pancreatic cancer "have a complex, intertwined relationship", note the study authors, with long-term type II diabetes being a risk factor for pancreatic cancer on the one hand, and patients with pancreatic cancer often being subsequently diagnosed with diabetes or impaired glucose tolerance on the other. Studies have also suggested a lower risk of pancreatic cancer among metformin users than in insulin or sulfonylurea users. Additionally, a study in breast cancer patients showed that diabetic patients receiving metformin had a higher response to chemotherapy than patients with diabetes who did not receive the drug [see also e-grandround on breast cancer prevention, p 17].

The aim of the current study, by Li Donghui and colleagues from MD Anderson Cancer

Center in Houston, Texas, was to determine whether metformin use conferred survival benefits. The investigators observed 302 patients with diabetes and pancreatic cancer, 117 of whom had been prescribed metformin.

Results show that the one-year survival was 63.9% for the metformin group versus 46.3% for the non-metformin group (P=0.002), with a two-year survival rate of 30.1% versus 15.4% (P=0.004). Median overall survival time was 15.2 months for the metformin group versus 11.1 months for the non-metformin group (P=0.004). Metformin use was significantly associated with longer survival only in patients with nonmetastatic disease.

"These data provide strong supporting evidence that metformin has the potential to be used as a supplemental therapeutic agent for non metastatic pancreatic cancer," write the authors. Considering the high prevalence of diabetes among patients with pancreatic cancer, and the lack of effective treatment strategies for this malignancy, they add, prospective studies should be conducted quickly.

The beneficial effect on cancer, suggest the authors, may be due to lower circulating levels of insulin as a consequence of reduced resistance, since it is known that insulin can play a key role in promoting cancer development.

In an accompanying commentary, Michael Pollak, from McGill University in Montreal, Quebec, writes, "We cannot exclude the possibility that patient characteristics that lead to a decision to treat diabetes with metformin rather than another agent are associated with a relatively favorable pancreatic cancer prognosis. In such a situation, metformin use would be associated with favorable outcome but not be responsible for it."

A rational combinations approach to trial design is needed, he adds, since it is possible that metformin might require pharmacologic optimisation for oncologic indications by improving accumulation in neoplastic tissue.

■ N Sadeghi, JL Abbruzzese, SJ Yeung et al. Metformin use is associated with better survival of diabetic patients with pancreatic cancer. *Clin Cancer Res* published online 31 March 2012, doi:10.1158/1078-0432.CCR-11-2994

■ M Pollak. Metformin and pancreatic cancer: a clue requiring investigation. *ibid*, published online 31 March 2012, doi:10.1158/1078-0432.CCR-12-0694

Survival trade-offs defined for prostate cancer treatment side-effects

➜ British Journal of Cancer

Severe urinary dysfunction and bowel symptoms were the least tolerable side-effects of treatment for localised prostate cancer, while severe hormonal effects and fatigue were considered more tolerable, and severe sexual dysfunction relatively benign, an Australian study exploring survival trade-offs of treatment has found.

For men diagnosed with localised prostate cancer, survival benefits from treatment can be offset by treatment complications, including problems with sexual, urinary and bowel function. But to date no studies have explicitly expressed patient preferences for treatment of localised prostate cancer in terms of the survival gains needed to make persistent adverse effects worthwhile.

In the current study, Madeleine King and colleagues, from the University of Sydney, Australia, set out to examine the survival gains that patients felt would justify different complications. Patients for the study were recruited from the Prostate Cancer Care and Outcomes Study (PCOS), a population-based cohort of men aged less than 70 years when diagnosed with prostate cancer, recruited from the NSW Central Cancer Registry, who were age- and postcode-matched to controls without prostate cancer.

A random sample of 357 men from a population-based sample of 1381 patients who had been recurrence-free for three years after being diagnosed with localised prostate cancer, and 65 age-matched controls without prostate cancer completed the preference survey. The survey considered the "hypothetical health states" of erectile dysfunction, loss of libido, urinary leakage, urinary blockage, bowel symptoms, fatigue and hormonal effects, each of which was rated as base, mild or severe. The questionnaire then included life expectancy, with levels 4, 8 or 12 years and ±25%, 50% or 75% respectively. Then according to patient answers, the survival gains needed to justify persistent problems were estimated from "an equation for compensating variation". The retrospective design of the study, write the authors, allowed men to bring "personal experience" to bear on their hypothetical choices.

Results showed that the survival gains needed for each adverse event were 3.25 months for mild fatigue, 4.00 months for severe impotence, 4.22 months for mild urinary leakage, 4.91 months for mild urinary blockage, 5.02 months for severe loss of libido, 6.22 months for mild bowel problems, 9.69 months for mild other hormonal effects, 12.33 months for severe other hormonal effects, 13.30 months for severe fatigue, 21.96 months for severe urinary blockage, 25.31 months for severe bowel symptoms and 27.69 months for severe urinary leakage.

"Thus we found that relatively modest survival benefits were sufficient to offset the most common side effects of treatments for prostate cancer for about two-thirds of the most common health states 3-years post-diagnosis," write the authors.

However, even substantial survival benefits were insufficient to offset severe urinary dysfunction, they add, which at three years was reported by 14% of their sample.

"Emerging evidence about survival benefits can be assessed against these patient-based benchmarks," write the authors. They point out that considerable variation in trade-offs among individuals underlines the need to inform patients of long-term consequences and incorporate patient preferences into treatment decisions.

■ MT King, R Viney, DP Smith et al. Survival gains needed to offset persistent adverse treatment effects in localised prostate cancer. *Br J Cancer* 14 February 2012, 106:638–645

Patients pay a price for spending cuts

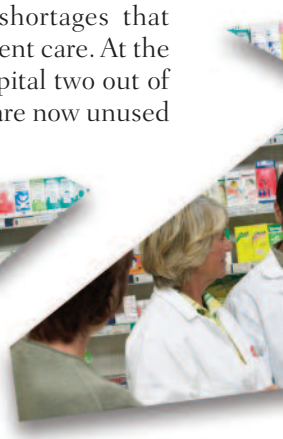
Anna Wagstaff

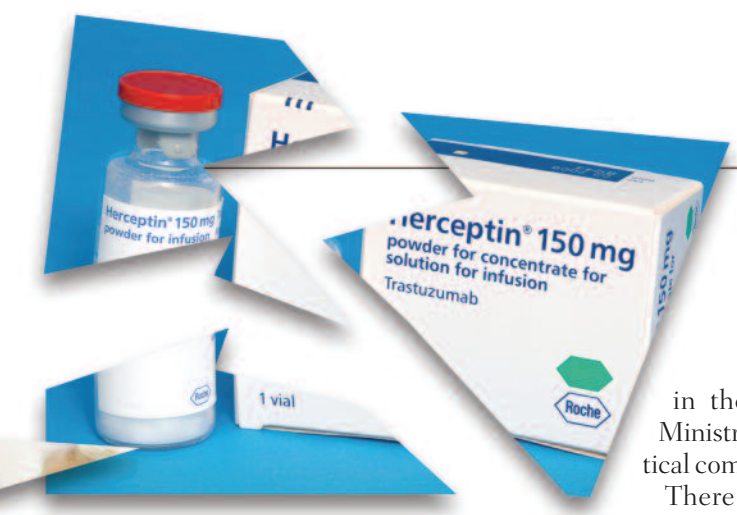
Austerity measures brought in to tackle the debt crisis are affecting frontline healthcare services in many countries, particularly in the complex, expensive field of oncology. *Cancer World* asked its readers to share their first-hand experiences.

Doctors are sounding the alarm about the price cancer patients are paying for dramatic cuts in public spending. In the countries hardest hit by Europe's debt crisis, services are hit from many directions at once: staffing cuts leave some operating theatres and linear accelerators idle, while patients flood into the public service because they can no longer afford private health insurance. Patients are also increasingly unable to get hold of drugs they need, as pharmaceutical companies withhold supplies due to unpaid bills – a problem which may be exacerbated by a growing re-export trade in which drugs bought at a lower price negotiated by debt-stricken governments find their way onto international markets to be sold at a profit.

John Spiliotis, a director and chairman of first department of surgery, and president of the scientific council of the Metaxa Memorial cancer hospital in Piraeus, Athens, describes the situation as working in "wartime conditions". His hospital has seen a 50% cut in its budget over the last three years, while admissions have increased by more than 30%. "If you compare these two figures, the conclusion is maybe we have a crisis in the management of cancer patients," he says.

Public sector employment rules that permit only one position to be replaced for every 10 that are lost are creating acute staff shortages that impact directly on patient care. At the Metaxa Memorial hospital two out of six operating theatres are now unused because there are too





few scrub nurses. The inevitable result is long waiting lists. Spiliotis says he just told a patient diagnosed with colorectal cancer to come back in 45 days.

Waiting times for radiotherapy are even longer, he says. In the four main cancer hospitals and nine other public hospitals with radiotherapy equipment, the waiting list is three to four months. "It is very difficult to propose neoadjuvant chemoradiation for patients with rectal cancer with waiting times like that. So the patient has to get this treatment from private practice."

Supplies of essential cancer medicines, including Taxotere, Temodal, Avastin, Herceptin and Mabthera, are drying up, says Kathi Apostolidis, a breast cancer and patients rights advocate. She describes driving around the hospitals and pharmacies of Athens for a friend, in search of supplies of Zometa (zoledronic acid for controlling bone metastases). Pharmaceutical companies are insisting on advance payment from hospitals and public health insurance, she says, while pharmacies are refusing to deliver medicines to patients on credit. She believes patients are being held hostage in the battles between the Ministry of Health, pharmaceutical companies and pharmacists.

There are worries too that financial concerns are leading patients to delay visits to a doctor. "We have a problem that 15–20% of patients do not consult a physician. We compared results from 2007 to 2009, and it seems that we are seeing cancer patients at a more advanced stage than three years ago, though we do not have statistically significant data on this as yet." If true, this would mean that not only are fewer staff having to care for more patients, using fewer resources, but a higher proportion of patients are presenting with cancers that are more complex, more expensive to treat and more likely to be fatal.

While Greece is undoubtedly at the sharp end of Europe's debt crisis, it is by no means alone. With austerity the prevailing watchword, public spending is being reined in everywhere. Although countries such as Spain, Italy, Portugal and Ireland are in the frontline, countries such as France, Belgium, UK and the Netherlands are not far behind. Even Germany, the strongest economy in Europe, has plans to cut public sector debt by €80 bn by 2014.

As healthcare accounts for a high proportion of public spending, and cancer accounts for a sizeable chunk of healthcare spending – with its need for complex multidisciplinary approaches to care, heavy use of expensive imaging techniques, and reliance on some very expensive drugs – cancer services are under pressure as never before.

For patients, many of whom at the best of times feel they have to fight for quick access to the best treatments, the most urgent question is to what extent the financial pressures on Europe's cancer services are affecting frontline care.

In an effort to answer that question, *Cancer World* asked its European readers for feedback on how the European debt crisis is impacting on cancer care in their own countries. Ninety responses from 20 European member states suggest that there is a strong perception that the debt crisis is having a direct impact on patient care well beyond the countries facing the toughest cuts (see box *overleaf*). Drawing on comments appended to the survey and on interviews with some of the respondents reveals a patchy picture across Europe, but patterns are emerging.

ALAMY, CORBIS

WHAT THE SURVEY FOUND

A survey of *Cancer World* readers, asking about how public spending cuts are impacting on frontline cancer care, attracted 90 responses from 20 of the 27 European member states. Overall only 10% of respondents reported no impact on the quality of care cancer patients receive, with the vast majority reporting "some impact" (around 40%) or "quite an impact" (around 35%), and a little under 15% reporting "a huge impact".

As might be expected, access to anti-cancer therapies (regardless of speed of access) showed the least impact, with almost 35% reporting no impact, a slightly higher proportion reporting "some impact" and only 25% reporting "quite an impact" or "a huge impact". Access to other types of care, such as supportive care and rehabilitation, appears to be taking more of a hit, with only 20% reporting "no impact" and more than 40% reporting "quite an impact" or a "huge impact".

Patients in many countries are also having to wait longer to get access to the services they need. The impact seems to be greatest for specific cancer therapies, such as surgery or radiotherapy, with almost 40% reporting a "huge impact" or "quite an impact" and only 20% reporting "no impact". But many patients are also facing longer waiting times for seeing a specialist and getting the necessary diagnostic tests (around 25% and 30% respectively reporting the top two impact categories).

Interpretation of these findings are subject to all the usual warnings about self-selection of respondents and the subjective nature of the responses.

Access to drugs

Access to certain cancer drugs is changing across Europe. Fatima Cardoso, director of the Breast Cancer Unit at the Champalimaud Cancer Centre in Lisbon, reports that some drug companies have started to withhold supplies from hospitals that have been slow paying their bills. The government has been trying to intervene in cases where the hospitals have no alternatives, but Cardoso expects this problem to get worse.

Some doctors have been reduced to lying to patients because they don't want to admit there is no money to pay for the drugs they need, she says. Cardoso cites the case of a patient whose bone metastases, which cause extreme pain and increase the risk of fracture, were being left untreated. "She had been told there are not enough data to support the use of bisphosphonates, because people are not frank enough to say: you should receive this drug but we have no money to give it to you."

As with Greece, public cancer hospitals and oncology departments in Portugal are finding themselves flooded with people who have had to give up private medical insurance. But even those who retain their private insurance can no longer afford the drugs they need, says Cardoso. "Even after so many years on the market, the price of trastuzumab is so shamefully high that most private health insurance barely covers the cost of one year of treatment, leaving nothing over to pay for the chemotherapy and all the other things patients need. For adjuvant therapy people sometimes do desperate things such as selling their houses to get the money for one year of treatment. But if you have to go on and on for as many years as possible, what can you do?"

In Italy, Anna Costato, who is being treated for advanced breast cancer, but is also a GIST patient advocate as a parent of a child with paediatric GIST, reports that access to new drugs takes longer and can depend heavily on where you live. This is because regional health authorities have the final say on what will be reimbursed, so a new medicine may be restricted even after approval by the European Medicines Agency and the national Italian agency AIFA.

Patients with rare cancers are hit particularly hard by measures that regulate the prescribing of drugs for off-label use. Costato believes that the measures, introduced in 2007, are now being wrongly used to restrict access to expensive drugs. She gives the examples of sorafenib (Nexavar), dasatinib (Sprycel), and nilotinib (Tasigna),

"People are not frank enough to say: you need this drug but we have no money to give it to you"

"In May, the value of an additional "quality-adjusted year of life" was devalued from €45,000 to €20,000"

which are recommended by the US National Comprehensive Cancer Network guidelines for patients with GIST who no longer respond to the only drugs approved for this indication, but which GIST patients have no access to in many regions of Italy.

Perhaps her greatest concern, however, is not so much the restrictions on medicines as the way financial pressures on doctors are leaving many patients feeling abandoned. "As an advocate of many patients with metastatic cancers, I find it very discouraging to realise that even some good oncologists are becoming more and more careful about spending money on treating terminally ill cancer patients." Their primary concern seems no longer to be helping them to survive, says Costato, but rather how much it will cost. "Doctors should stay on their patients' side," she argues, "helping them to obtain proper treatments. and advocating for them, if necessary. They should leave accountancy to the accountants."

In France, a country that has long prided itself on being at the forefront of adopting new cancer drugs, medical oncologist Jean-Yves Blay says the authorities appear to be quietly implementing a far more restrictive approach. A sarcoma specialist, he gives the examples of pazopanib (Votrient) and mifamurtide, which have both been rejected by the Commission de Transparence (which plays a role in reimbursement decisions in France) despite having been accepted for reimbursement by the UK's NICE, which has tended to operate one of the more restrictive policies in Europe.

His worry is that this move towards – and beyond – NICE levels of restriction does not seem to be accompanied by similar levels of transparency, making it hard to comprehend or challenge decisions. "What isn't clear in France is the process. Why is it being rejected? This is particularly shocking in the case of mifamurtide, which was reported to improve survival in one of the largest academic trials in osteosarcoma, admittedly with some methodological questions. This is a compound that is relevant to only around 100 patients per year. Yet the decision on this has left the drug in some sort of limbo – nobody can even buy it outside the system and give to a patient in France, meaning that we academics cannot even study it further. I had never seen that before in France."

Ireland, meanwhile, has taken the slightly shocking, but arguably less opaque, step of more than doubling the height of the bar that new drugs have to jump before being accepted for reimbursement. In May, the value of an additional "quality-adjusted year of life" or QALY, which is used as the main measure to decide on reimbursement, was devalued by executive decision from €45,000 to €20,000 – a level which by today's standards would seem completely unrealistic for new cancer drugs. There will doubtless be some room for manoeuvre – following a public campaign, Yervoy (ipilimumab) for melanoma was recently approved on the basis of a QALY that was negotiated down from €150,000. At best it seems cancer patients who want access to new drugs may to have to fight for it on a drug by drug basis.

Respondents from a number of countries also mentioned possibilities for running clinical trials – with all the associated advantages in terms of pushing up standards of care and early access to drugs – are increasingly restricted as a result of a more restrictive approach to new drugs combined with overstretched staffing.

ALAMY

Who cares? There are concerns in some countries about the adequacy of care available to patients who are being sent home early to save hospitalisation costs

Levels and quality of staffing

Staff shortages and/or the de-skilling of certain roles due to budget cuts was another theme mentioned by many respondents.

In Portugal, waiting times for radiotherapy at public hospitals have been the focus of highly critical press coverage, because there are too few staff to operate facilities to full capacity. Patients are being badly let down says Cardoso. "I recently had a patient who had intensive bone metastases in her spine, particularly the cervical spine. She had been waiting for more than three months for radiotherapy. In the meantime, she developed leptomeningocarcinomatosis [affecting the tissue that covers the brain] and she is dying, at 37 years old." Cardoso believes that while poor prioritisation of patients and poor organisation may be partly to blame, lack of personnel is also an important cause.

Costato in Italy talks of a steady decrease in the number of nurses, alongside a decrease in the number of hospital beds and length of hospital stays. What concerns her is that the care patients get on leaving hospital is largely given by low-paid untrained workers, which is impacting on the quality of care. Staff hiring is effectively frozen in hospitals, she says, which makes itself felt in longer waiting times for CT and MRI scans and for consultations with oncologists. Massimo Conio, a gastroenterologist in Sanremo, Italy, reports similar increases in waiting times for surgical procedures. Other survey respondents talk about staff shortages impacting on access to supportive therapies, "reducing the possibility of supporting the quality of life of children and families."

Ingrid Kössler, a breast cancer patient advocate involved in Sweden's National Cancer Control Strategy, reports similar concerns over the increasing use of less trained nurse-assistants in place of nurses. Staffing is so tight, she says, that hospitals have come to rely on student nurses to cover absences during summer holidays. This year the student nurses are refusing to work unless they are paid a full salary; it is not clear how that will be resolved.

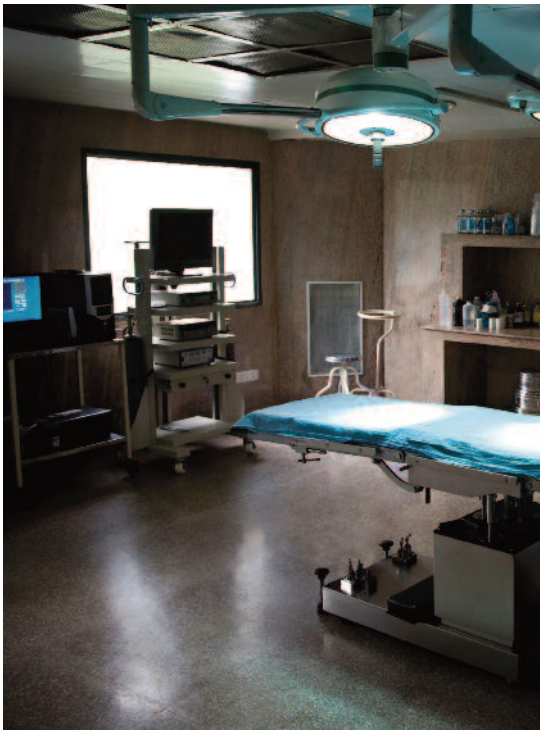
A scandal centred in Gothenburg over 60 patients with melanoma who were wrongly told they did not have cancer has put a spotlight on the strains personalised medicine is putting on pathology departments. Pathologists point out that they are being asked to perform many more tests for many types of patient than was the case a few years ago, and at current staffing levels they are finding it hard to cope. While Sweden is not one of the countries hardest hit by the debt crisis, says Kössler, the ageing population means that while cancer and other age-related chronic diseases are putting a greater burden on the health budget, there are now only two people working – and paying taxes – for each retired person, compared with a five-to-one ratio a few decades ago. A stagnant economy is not helping.

Comments from Ireland talk about a reduction in the number of "allied professionals" involved in the delivery of cancer care, including psychological support. A lower staff-to-patient ratio means less time spent with patients.

In the UK, survey respondents talk about reductions in follow-up visits and cutbacks in specialist breast nurses, scrubbed nurses (for operating theatres), "team members" and the administrative support necessary to free up clinical practitioners from bureaucratic functions. Nursing staff made it very clear at a recent conference that, in their experience, frontline clinical care is being directly affected by staff cuts despite assurances from the government to the contrary.

In the Netherlands staff cuts are reducing the healthcare support available to care for patients in their own homes.

Survey respondents from Spain mention longer waiting lists for diagnostic procedures and consultations with a specialist, as well as greater restrictions on access to health care from home support teams. Though it's hard to quantify, it is clear that staffing levels are being steadily eroded through a virtual freeze on new appointments combined with the loss of many staff who were on fixed-term contracts. Cuts of 10–20% are planned for hospital staff who are not directly



ALAMY

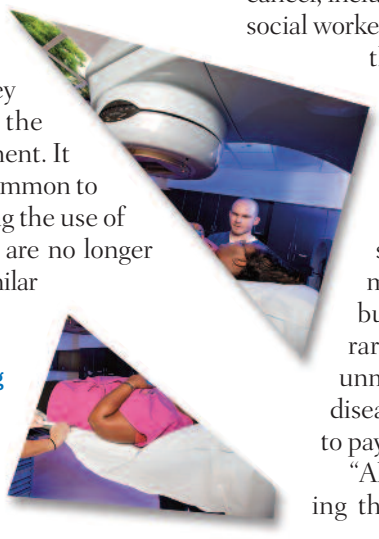
"Every Friday we have news about what the government is going to do – it is really horrible for us"

employed by the state (about half of the workforce). But Eugenia Trigoso, a nurse specialist in paediatric haematology in Valencia, believes the worst may be yet to come. With Spain's economy exposed to a crisis that seems to have no end in sight, she says the real worry is what they don't know. "Every Friday there is a cabinet meeting and we have news about what the government is going to do. It is really horrible for us, what is happening now."

Costs and benefits to patients

Responses to the survey also indicated that patients in many countries are being asked to pay more towards their care and/or losing some of the social benefits they can expect to receive. In some cases the extra contribution is fairly minor – a few euros per hospital visit – and would be unlikely to impact on their care. In other cases there are concerns that additional charges may have a real and negative impact, for instance if they result in later diagnosis because patients delay visiting their doctor, or if the patient opts for cost reasons to forego medicines or services that could help them.

Many countries, including Spain, Portugal, UK and the Netherlands, are cutting back on reimbursement of transport costs for hospital visits. In the Netherlands, medical oncologist Elisabeth de Vries reports that patients requiring access to physiotherapy now have to pay for the first 20 treatments themselves, at €30/session, though patients with 'chronic' problems are exempted. Access to a dietician may be removed from the reimbursement list, and patients now have to pay for many of the self-care medications they need to cope with the side-effects of treatment. It is becoming more common to see patients foregoing the use of wigs, because these are no longer fully reimbursed. Similar issues are reported from Ireland.



Wasted capacity. Staff shortages mean operating theatres and radiation facilities lie idle while patients have to wait longer for treatment

Cuts and restrictions in the benefits available to cancer patients seem to be a feature across many countries in Europe. In some countries these are hitting patients on oral therapies disproportionately, and in others they are also hitting families of paediatric patients. Though these cuts may not directly impact on the quality of healthcare patients receive, they could further deter some patients from accessing therapies and services where they have to cover or contribute to costs.

Where next?

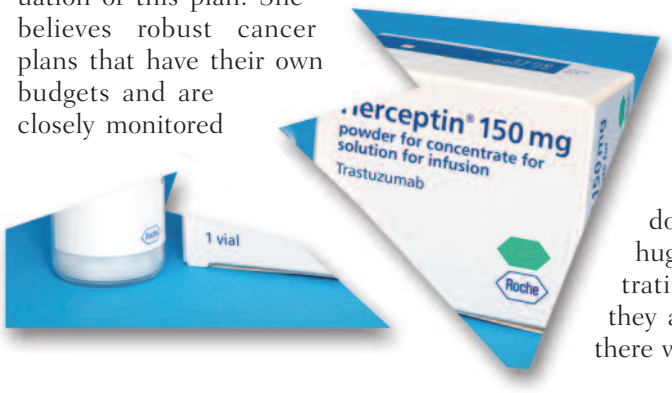
Elke Van Hoof, head of the Belgian Cancer Centre, which coordinates the Belgian Cancer Plan, is convinced that having a detailed, fully budgeted cancer plan, subjected to continuous evaluation has been an important factor in protecting all aspects of cancer control from spending cuts. Over the past 10 years, she says, Belgium has invested a lot in cancer, including in more psychologists, social workers and nurses. She is proud that last December the new government reconfirmed the budget previously agreed for the Belgian Cancer Plan. Despite the financial crisis, she says, the government even allocated an extra budget for early and temporary access to therapies for unmet medical need and rare diseases, as well as extra money to pay for nutritionists.

"All the stakeholders, including the government, are trying

to keep the budget for care as it is now," she says. "We are told not to spend extra, but to try to be creative with what we have, so we are really evaluating the way we are reimbursing. Can we reduce the costs of reimbursement if we increase efficiency? Can we economise to have new funding to do new things?"

Greater integration is one focus point. "We pay for psychologists in cancer care, but can we also use them for other things?" Evaluating value for money is another. "Breast implants are very well reimbursed in Belgium, but they have a risk. Might it be better to use breast reconstruction with own tissue – isn't it more efficient because you have fewer complications and procedures in the longer term?" The option of adapting levels of reimbursement to encourage use of generics rather than expensive brands, where appropriate, is also under consideration.

One important spin-off of this proactive approach, says van Hoof, is that the Belgian Cancer Centre is able to back up its proposals for actions to include in the Cancer Plan with strong arguments and detailed data derived from the continuous evaluation of this plan. She believes robust cancer plans that have their own budgets and are closely monitored and evaluated will be key to safeguarding the best quality care for cancer patients as Europe moves forward. She is glad that in Belgium they managed to get such a plan up and funded before the debt crisis struck.



But what of the countries that didn't? In Greece, John Spiliotis fully accepts that decades of virtually uncontrolled spending on healthcare, with the highest doctor-to-nurse ratio in Europe and no restrictions on prescribing, has contributed to the current crisis. He recognises the importance of a more sustainable, planned approach to delivering cancer services; he welcomes prescribing guidelines and greater use of generics; he is committed to cutting the list of lab tests, shortening the list of imaging procedures, cutting hospital stay, and using palliative rather than aggressive treatments near the end of life. He and his fellow surgeons are even shunning expensive technologies where it is safe to do so, going back to the manual procedures they haven't used for years, just to cut costs. "But we can't turn the clock back to the '60s or '70s in cancer treatments," he says. "This is a big problem that started 30 years ago. We cannot correct it in the three to five years that Europe is demanding of us."

In Portugal, Cardoso believes there is huge scope for concentrating resources where they are most needed. "If there were proper guidance so governments understand how to calculate overall cost-effectiveness, rather than just looking at the price of drugs, I think we could cut at least one third of the cost without affecting the quality of care," she says, "and we have to do it wisely and in a fair way." That guidance, she adds, has to come from collaboration between health economists and the people who deliver frontline care.

She is acutely aware of how much money is being wasted, for instance when vials of expensive drugs are opened, partially used, then thrown away because guidance says they can't be stored once opened. Coordinating things so that all patients receiving these drugs get them on the same day would help. However, drug companies must also cooperate in providing accurate data about the stabilisation of drugs and time-frames for use, she says.

In her own particular area, Cardoso is now focusing her efforts on advocating for all patients to be treated in breast units. "If you centralise treatment with people who know what they are doing, they will spend less," she says. She is also encouraging patient groups to speak with one voice and focus their demands on the bare essentials: access to best treatments; no cuts to medications that cannot be replaced; no cuts that affect the quantity and long-term quality of life.

"If you centralise treatment with people who know what they are doing, they will spend less"

"This problem started 30 years ago. We cannot correct it in the three to five years that Europe is demanding"

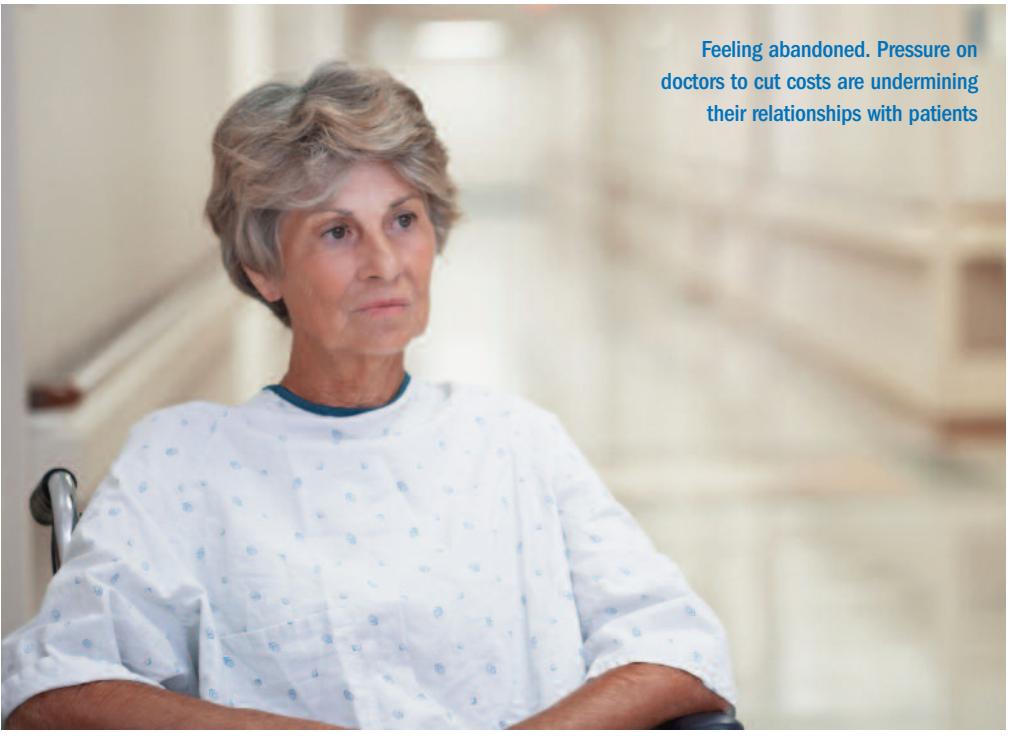
While she is more than ready to pull her weight within her own specialist area, Cardoso says this crisis cannot be resolved sector by sector. "You have to look at the whole picture. There are things you could really cut down, and others that you can't because there is no option." She questions, for instance, the high use of statins. "Statins are prescribed with no control at all, and are very often overused."

Right now, however, patients in Portugal are threatened with the same crisis in getting hold of essential anticancer drugs as is already happening in Greece, and they need an urgent solution. Cardoso would like to see efforts, probably at EU level, to broker an agreement with pharmaceutical companies that would allow hospitals that have been pushed into massive debt by the cuts to spread their payments over a longer time period. Even in the longer term she questions whether the current high prices of medicines are sustainable. "This is not just affecting Greece or even Portugal, Spain is already affected and it will soon start affecting Italy and France. This is a pan-European problem and we need a larger solution. Even if we think of it as a business problem, if the majority of countries are not able to pay, they are not going to sell."

One possibility, she suggests, might be for the EU to expand the investment it already makes in supporting pharmaceutical development, "in return for which the companies could put the drugs on the market at a lower price."

There's no question that this is a pan-European problem. The issue of how European countries – with ageing populations, a growing burden of chronic diseases, and rising costs of cutting-edge treatments – can provide the best possible care on a more sustainable basis has been around for decades. The current debt crisis and consequent austerity drive has merely brought it to a head, and whichever way the debates about austerity versus growth may go, healthcare rationing is now a reality.

Does that mean doctors will be forced to turn into accountants and put affordability before the interests of patients? Paradoxically, if the experience in Belgium as described by van Hoof is anything to go by, thinking more like accountants may be the only way doctors can safeguard their ability to fight for the needs of every patient. But instead of looking at a patient and wondering whether genuine opportunities to extend or improve their quality of life represent value for money, they need to be doing a lot more detailed monitoring and evaluation of the effectiveness and value for money of the treatments and types of care they deliver. Doing so will not just maximise the benefit patients get for the money spent but, as van Hoof showed, it also gives doctors and advocates essential evidence to help them argue for the level of resources they need… and to defend those budgets when they are under threat.



Feeling abandoned. Pressure on doctors to cut costs are undermining their relationships with patients

ALAMY