Cancerworld

Education & knowledge through people & facts

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Paolo Casali

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A window of opportunity

Kathy Redmond ■ EDITOR

Millions of people will die unnecessarily unless a massive effort is made to tackle the worsening global cancer epidemic. But the investment in cancer control that is so desperately needed, particularly in low- and middle-income countries, will not happen until cancer control becomes a development priority. The momentum generated by the launch of the World Cancer Declaration in Geneva this August offers an opportunity for galvanising people into action that we cannot afford to squander.

The failure of health organisations to grasp the seriousness of the situation is graphically illustrated by an article in *The Lancet* (27 September), which flagged up the deadly disconnect between what needs to be done according to public health evidence and the priorities of the largest international health-care donors – the World Bank, the US Government, the Bill and Melinda Gates Foundation and the Global Fund for HIV/AIDS.

These donors have a huge influence over national health priority setting and resource allocation, particularly in countries that are dependent on aid – in some sub-Saharan states, for instance, 40%–60% of national health-care expenditure comes from donations. But the failure to match fund allocation to needs means that, while cancer kills more people than AIDS, TB and malaria combined, in 2005 the biggest international health donors allocated only 2% of funds to chronic diseases. This represents about $3.2 per death, compared to HIV/AIDS, which received more than $1000 per death.

Only the World Bank invests in long-term initiatives to support improvements in health systems as a whole – an approach that can help improve outcomes for all diseases, not just a select few.

The biggest problem we face in securing greater investment in cancer initiatives is that most donor agencies set their priorities based on the Millennium Development Goals, which give barely a passing reference to reducing the burden of chronic diseases. The World Cancer Declaration sets out to remedy this disastrous oversight, calling for cancer to be put squarely on the development agenda and for cancer control policies to be given priority as a key strand of investment in a country's economic and social wellbeing. The cancer community now needs to embrace this Declaration and put pressure on governments, NGOs and leading donor agencies to develop strategies to meet the 11 targets outlined within the next 12 years.

Establishing a Global Fund for Cancer, comparable to the Global Fund for HIV/AIDS, would also send out a clear message that cancer is a key global health threat and provide valuable resources to kick-start projects in countries in greatest need.

The World Cancer Declaration is supported by almost 500 international cancer organisations and 3,500 individuals. To read the Declaration and add your support, visit http://tiny.cc/worldcancerdeclaration

Paolo Casali:

the man with the method

Marc Beishon

Paolo Casali specialises in sarcoma, a 'rare' cancer with at least 50 subgroups. Good practice, he believes, starts with a deep knowledge of the disease in front of you. This, in turn, requires a rigorous approach to clinical methodology – something he feels the cancer community should pay more attention to, for the benefit of both patient care and clinical research.

The first point any oncologist makes about rare cancers is that they are – collectively at least – not rare at all. As Paolo Casali, the medical oncologist head of the adult sarcoma medical unit at the Istituto Nazionale dei Tumori – National Cancer Institute – in Milan, states: "Even if you use very conservative definitions, at least 20% of all tumours are classed as rare – and together the whole group makes up the same number as two of the big killers. But the misconception that this group is rare means we have great difficulty getting resources to treat them."

That misconception plays out to the disadvantage of patients in a number of ways, in particular lack of specialist centres for rare cancers and poorly coordinated research efforts. While outlying hospitals may be at a disadvantage for many tumour types, a lack of a specialised multidisciplinary team can be especially acute for diseases that are not seen on a day-to-day basis. Some rare cancer groups have made substantial progress in networking – leukaemia/lymphoma being a good example – but as Casali points out, there is as yet no fully fledged international network for adult soft tissue sarcomas, a group of diseases that he says is as common as adult leukaemias.

"In fact, all rare solid tumours are, if anything, more frequent than haematological tumours, and they should be a priority now," says Casali. "It is simply that the haematological institutions have been used to collaboration for longer and their networks are more advanced." That's not to say that sarcomas do not have a good deal of dedicated activity – as he adds, there are national groups in most major countries, and he comments that there is a close knit, if relatively small, worldwide community of sarcoma researchers. "Despite some long-standing controversies on certain treatments, there is a strong consensus within this community," he says.

Meanwhile, there are encouraging developments on the wider European stage. In 2007, the European Commission (EC) started a public consultation on the challenge of all rare diseases, and submissions were received in February this year. Naturally, the oncology community made several contributions, notably from the European Society for Medical Oncology (ESMO), where Casali is the current treasurer, and RARECARE, an EC-funded project for the surveillance of rare cancers in Europe, led by

ELIGIO PAONI

Gemma Gatta, an epidemiologist in the Milan institute, which Casali is also involved with. And in 2006, CONTICANET, a Network of Excellence funded by the EC's 6th Framework Programme, was set up to start to address the fragmentation in sarcoma work, but is, as Casali says, only at an early stage.

Other important issues that also concern Casali may be harder to address. Chief among them is the availability of approved drugs for use with rare cancers, and the role played by regulators and pharmaceutical companies. Another key topic is the conduct of clinical trials, where regulation again could come into play to increase the clinical relevance of results. "There is much interaction between regulators and the pharmaceutical industry, and between clinicians and the drug firms, but we are missing a third side of the triangle – between ourselves and the regulators, which could help influence study design and drug availability," he comments.

Above all, given the challenges of rare cancers, Casali wants to promote far more effective networking among clinicians, and cites among his most important projects contributing to the regional network for all types of cancer in the Lombardy region of Italy, where Milan is located, and developing the Italian Network on Rare Tumours, for which he is the coordinator. The latter connects the work of Italy's major cancer centres on adult solid tumors, and Casali is keen to emulate the more advanced networks seen in countries such as Sweden.

"We are missing interaction between ourselves and the regulators, which could help influence study design"

Focusing on optimal care is of course a priority, especially in a 'long' country such as Italy, where patients may have to travel far to find a specialist. "Sarcomas are non-epithelial tumours of connective tissue – most solid cancers are epithelial in nature – and they can arise anywhere in the body," says Casali. "So we are not organ specific. The main treatment is surgery, and good practice may be crucial for the best outcomes for sarcoma patients." Soft tissue sarcomas often appear easy to excise, he adds, and as most soft tissue masses are benign, some surgeons do not even consider the possibility of malignancy, which can result in inappropriate treatment and late referral to a specialist. "In the UK they call it the 'whoops' surgery – the surgeon cuts and then says, 'Whoops, it was a sarcoma.'"

While Casali's institute will see about half of all Italy's soft tissue sarcoma patients at some point in their history, it is common to find that suboptimal surgery has been done. "It may not affect their prognosis but they may need several additional and unnecessary operations, and suffer outcomes such as loss of limb function. But it is much harder to transfer knowledge to local hospitals about rare diseases, as you need to reinforce your learning constantly."

His institute in Milan has a dedicated sarcoma surgeon and is of course multidisciplinary overall, with integrated radiotherapy, medical oncology and pathology. "One of the main added values of our networking has been to change a lot of pathology diagnoses – the importance of pathology in groups of rare and complex tumours can't be overestimated." He mentions Paolo Dei Tos, an internationally known sarcoma pathologist who works in a small town north of Venice, as someone who plays a crucial role within the network to improve the quality of sarcoma diagnoses.

And because sarcomas are a collection of some 50 or so subgroups of tumour, Casali considers the investigational approaches to finding treatments for subtypes such as GIST are also serving as models for the more common cancers, as they too are rapidly subdividing into their own subgroups. "Even frequent tumours may become rare tumours," he says. But there have been considerable methodological problems about some studies on sarcomas so far, reports Casali, "such that in our clinical practice we tend to do the opposite of what some of the major cooperative trials have suggested," for instance regarding the use of adjuvant and multi-therapies in advanced sarcomas.

So like many research-oriented oncologists, he is right on the cusp of all the key issues and uncertainties about progress in targeting subgroups – and sometimes subgroups of subgroups – in cancer patient populations. However, there is one point on which he is crystal clear, and which has been his mission for some time – the need for a deep understanding of the disease in front of you. "Being disease oriented and not drug oriented is my starting point as a medical oncologist."

Casali is one of those oncologists who always wanted to be a doctor, despite having no medics in his family. But like many, his path into oncology was mainly by chance. "In my last year of university I had done the usual round of surgery, internal medicine, neurology and so on, and finally I came to work at the National Cancer Institute, and I found it a very interesting environment. Back then, there was only one medical oncology department, but it was led by Gianni Bonadonna, the most famous Italian medical oncologist, and he promoted an openness that was hard to find elsewhere, and still is to some extent in Italy."

By openness, Casali means an environment where clinicians and researchers were encouraged to collaborate on an international basis. And Bonadonna, a pioneer in the adjuvant treatment of breast cancer and the development of the combination chemotherapy regimen that remains the gold-standard treatment for Hodgkin's disease, made a big impression on Casali. "Being in contact with the outside world was a big draw for me. Yes, it can be better for young clinicians to work abroad and develop connections that will last for life – I've had to work hard to do so from here – even if you won't find anything very different in the clinical approach elsewhere."

Casali worked as a clinical fellow and associate

"Being disease oriented and not drug oriented is my starting point as a medical oncologist"

physician for nearly 10 years at the Institute, and then another 10 years in a full staff position as a medical oncologist, before being made head of the adult sarcoma medical treatment unit in 2004. His focus on sarcomas developed gradually over this time, and finally became his exclusive focus. In fact, his first board certificate was in haematology, before he went on to be certified in clinical oncology, and initially he was assigned to work mainly on lymphomas.

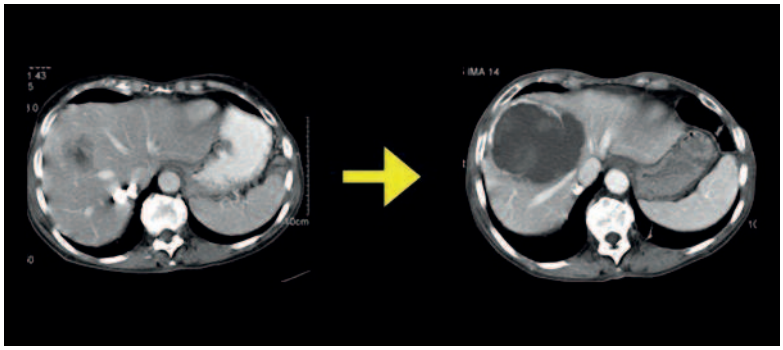
"I started looking at sarcomas in the late 1980s, when a decision was made that I would follow the disease from the clinical research standpoint. The same day I went to the library and made photocopies of all I could find on sarcomas and started studying the subject in depth – and if you do that you can start really enjoying the experience.

"I remember at the time doing my outpatient clinics on lymphomas, that the more in-depth I went on sarcomas, the more I felt I understood lymphomas. If you understand one disease in detail you are in a good position to understand others – and that's probably because of appreciating how clinical methods work."

Casali's interest in the 'clinical method' is long standing, and indeed way back in 1991 he co-authored with Lisa Licitra and Armando Santoro a book on the topic, published in Italian. "I found that looking at the issues concerning clinical methods was very helpful to both my clinical practice and research – we looked at concepts such as tumour response, quality of life, staging, follow-up and so on – all the areas that have to do with clinical methods in oncology. As two young oncologists at our world-renowned institute, it struck Lisa and me that no one had paid much attention to many of these issues, and it is still a problem."

He takes tumour response as an example. "I feel that the medical oncology community has not approached this from a conceptual point of view, relying instead on convention. Tumour response was defined by David Karofsky as a 50% decrease in the main area of a lesion, but there is no reason why 49% or 51% is not a response. The convention is not based on clinical or biological grounds – it's just a way of talking about the same thing, and nothing much has been done to refine the convention."

With the new targeted drugs, the problem has become clear. As a graphic illustration, he shows before and after slides of liver lesions from a GIST patient who has received Glivec (imatinib), where in the second the lesions are bigger. "But if you do a biopsy you don't find as much tumour and the patient is actually responding. Using the Karofsky definition, it would be seen as a progression not a response."



A question of method. Using the standard RECIST measure of response, this liver lesion appears to have progressed on a CT scan, but a biopsy would reveal the opposite to be the case

It is one element of understanding how this sarcoma subgroup works, and of course one of the great success stories in targeted therapies is Glivec and GIST. Because of its similarity at the molecular level to chronic myeloid leukaemia, GIST was the logical second tumour to research for the drug, and trials have shown major survival in those with advanced cancer.

Casali stresses how important it is to take a disease-oriented, clinical approach to treatment and research, especially with groups such as sarcomas. "While we have big improvements in GIST, in other sarcomas it has been difficult to show gains with drugs because the main treatment is surgery. But if you look at the Eurocare data, big differences were shown in the past between west and east Europe, which must depend on something – mainly the multidisciplinary approach, although that's hard to prove as you have selection biases when comparing centres. But I feel quality of care and multidisciplinarity must mean something – and here in Milan, for example, our sarcoma surgeon Alessandro Gronchi is directly involved in helping to highlight the activity of drugs, and we are involved in his work."

This disease focus has led to clinical practice that is at odds with the results of some sarcoma chemotherapy trials, particularly the large trials such as those run "very rigorously" by the European Organisation for the Research and Treatment of Cancer (EORTC). "Many sarcoma oncologists tend to favour adjuvant chemotherapy and multiagent chemotherapy in advanced disease, which are the

opposite conclusions of the trials," he says. Meanwhile, particular contributions his team has made include clinical observations of response to trabectedin (Yondelis), a new marine-derived drug, in myxoid liposarcoma, and of Glivec in chordoma, a very rare type of sarcoma. "When we treated the first patient with advanced chordoma, it was only when we looked at the slides in the same way as we'd learnt to do with GIST that we understood he was responding," he adds.

The reasons he and also others choose not to rely on the major randomised cooperative trials mainly concern the limitations of applying findings of large-scale trials directly to the bedside. Two issues, in particular, are lack of specificity in the study populations – mixing high- and low-grade tumours for example – and lack of clinical input to the study designs, such that biases about aspects such as surgery may be present. "It is often the case that clinicians are not involved in the methodology of clinical studies as much as they should be – we often don't understand the language of medical statistics and so do what the statisticians say."

This is not to say that the major trials are not valuable – Casali is a leading participant and coordinator in existing work and a strong advocate of much larger and inevitably more expensive intergroup studies. But, as he, with Licitra and Paolo Bruzzi, noted in an editorial on reporting clinical trials and meta-analyses (*Annals of Oncology,* August 2000), clinical decisions are very complex and are influenced by many factors, and oncologists need to take into account other sources such as phase II studies, case series, and much other descriptive knowledge. Randomised trials also provide more information than the simple '*P*-value', while of course randomised studies with sufficient power will never be carried out on a lot of clinical issues, especially on rare tumours. A new clinical method that tailors evidence to patients, often with elements of subjectivity, is needed – a proposition that formed the basis of the editorial.

In turn that means open discussion with patients about the uncertainties with treatment, quality of life and cost. Casali is involved with drawing up ESMO's sarcoma guidelines but is also one of the organisers of START – State of the art oncology in Europe – a website that has tumour-specific information designed, he says, to help doctors and patients explore a more individualised approach. START is administered from Milan but has a Europe-wide input (see startoncology.net). As an example of how finely balanced one of sarcoma's enduring controversies is, he mentions a 'for and against' debate on adjuvant chemotherapy at an ESMO conference in Istanbul. "I spoke for, and Ian Judson of the Royal Marsden against, but we agreed that we were using essentially the same slides with the same premises. Overall there is a broad consensus in the sarcoma community, although the clinical decision for the individual patient may be different. But this is not a problem, as long as the patient is involved in the uncertainty of decision-making."

At national and European levels, Casali would also like to see regulators setting out in more detail how clinical trials should be conducted. "The design of trials should be as targeted as the drugs are – and as the regulators share study designs with the pharmaceutical companies they can influence them from the start by listening more closely to the research communities." Without more direction, he feels the methodological problems of investigating subgroups in rare tumours will continue to be a major issue, and costs of new drugs will be unbearable if their use is not 'targeted'.

Then there is the issue of availability of both new and old drugs for rare cancers, and here Casali makes two key points. "First, we now have rules on orphan drugs that give incentives to pharmaceutical companies to develop drugs for rare tumours. That's an achievement the European Medicines Agency and the EU must be proud of. But the incentives only apply to approved drugs, and companies may decide not to register drugs if they feel the risk of trying to provide the same quality of evidence as that required for trials on more frequent tumours is too high.

"There then follows the big problem of off-label

"A new clinical method that tailors evidence to patients, often with elements of subjectivity, is needed"

"Oncologists take on a higher, and possibly legal, responsibility when they use off-label drugs"

use, which is very common in oncology. It does not just involve new drugs – there are a lot of older drugs which companies will never ask to have registered for certain tumours now. But the industry is the only party entitled to register a drug." His concern is that oncologists take on a higher, and possibly legal, responsibility when they use off-label drugs, and that varying patterns of reimbursement and policies for allowing their use will give rise to inequalities around Europe. "Each country is trying to address this problem differently."

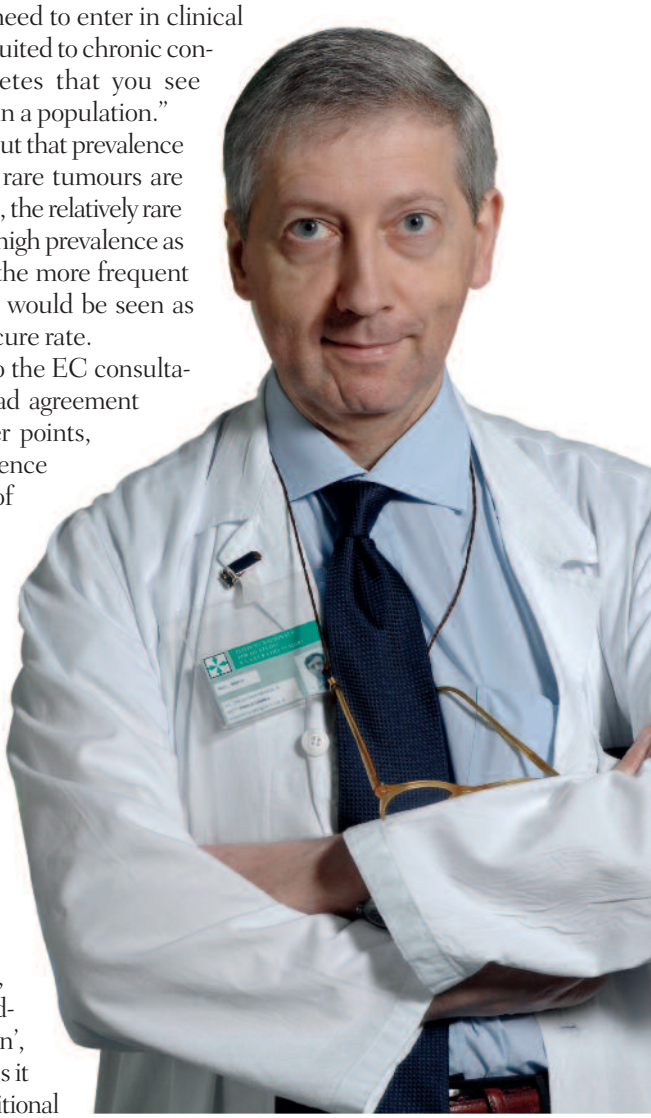
There are, for example, certain off-label cytotoxic chemotherapies that are showing activity in sarcoma subgroups, and Casali feels the best way forward is to establish standard medical compendia that, in practice, give a green light to the use of some off-label drugs. This is in place in some European countries, and also in the US, where it was set up by the state Medicare programme, but is also broadly followed by private insurance agencies. That this is a big issue is evidenced by an editorial Casali wrote last year on behalf of ESMO in the *Annals of Oncology* (2007 18:1923–25), and he says the society will be surveying oncologists to gain a more detailed picture of how policies differ around Europe.

In fact ESMO is very much taking this and other issues to decision makers at the European level. Having succeeded this year in getting a European Parliament resolution passed on EU-wide recognition of medical oncology as a specialty, their main priority is to get this implemented. Other efforts include highlighting issues with rare and difficult-to-treat cancers, which will be the subject of an event hosted by ESMO in Brussels in early November. Casali and colleagues intend to put drug availability and related issues to the fore, including a discussion on improving the methodology of the development of new drugs for rare tumours.

Clearly, the recognition by the EU that rare diseases need particular attention is welcome, but as Casali notes, the very first part of the consultation exercise – defining what a rare disease is – immediately becomes a problem for oncologists. "The definition is based on prevalence of disease, not incidence," he says. "While we must respect prevalence as a definition – the rules on orphan drugs are based on this – incidence is much more appropriate for cancer, as events only happen once in this disease. Incidence allows us to estimate the number of people, say, having surgery and first-line chemotherapy, and also the numbers we need to enter in clinical studies. Prevalence is suited to chronic conditions such as diabetes that you see through people's lives in a population."

Further, he points out that prevalence can greatly skew how rare tumours are identified – for example, the relatively rare testicular cancer has a high prevalence as it is very curable, but the more frequent small-cell lung cancer would be seen as rare, thanks to its low cure rate.

In its submission to the EC consultation, ESMO is in broad agreement with most of the other points, such as setting up reference networks – which of course cannot come fast enough for Casali. CONTICANET, which is headed by his good friend Jean-Yves Blay, professor of medicine at the Université Claude Bernard in Lyon, "could be the embryo of a soft tissue network at last." It aims to overcome difficulties with 'lack of data, mobility of researchers, heterogeneity of methodologies and legislation', and Casali has big hopes it will help overcome traditional



obstacles to pan-European working. He sees regional collaborative networks, where patients are managed over a wide area, as crucial to avoid 'health migration' to centres such as Milan, with consequent long waiting lists.

Even in one of Italy's premier cancer centres, however, there are major resourcing problems. Casali's sarcoma unit, for example, has ten physicians, but only two – himself and long-time colleague Rossella Bertulli – are permanent staff. The rest – among them international names in the sarcoma community – are funded mainly by research money. It is not surprising that when he is not on international work Casali spends most of his time in the clinic and in tumour board and pathology meetings, and other activities in his unit. His one other internal role is secretary of the Institute's ethics committee for clinical trials, which he says gives him insights into issues such as how samples from hospitals that may contribute only a few patients can be controlled by the sponsors, leaving academic researchers such as biologists out of the picture. "We are debating in Italy now how tumour samples are used in clinical studies," he says.

An advantage of working with rare cancers is, however, that pharmaceutical companies are more open to direct collaboration with clinicians. "It's a privilege for us because the sarcoma community is so small and, of course, we can also try methodological solutions that are not followed in more frequent diseases, which again is why I further believe we can be a model for oncology as a whole."

Casali does a little teaching at postgraduate level and says young oncologists are wary at first about working with rare tumours. "Then they find that you can learn clinical methods no matter what disease you work on and that it is great to go into depth." No doubt he is keen to be a good role model for his thinking on the clinical method – when asked to cite mentors, he can more readily suggest people who showed him what not to do. "I've found a lack of interest in clinical methods, but what worries me most are people who are too conservative and don't want to try new things." Running up against such department heads has been his main professional barrier, he says. "Although by instinct I am a bit conservative myself, I always wonder how to change things."

People who will be doing less wondering and taking more action, says Casali, are patients. "We can now add advocacy groups as a third category of trial sponsor to the industry and academic sectors. I believe they will drive a lot of research in future. More and more patients will not join studies that the groups do not approve of and this will be critical for pharmaceutical companies, which are also supporting these groups. It's a complex scenario, with potential conflicts of interest. But doing anything always implies conflicts of interest – disclosure is a good remedy."

A patient-driven study he mentions investigated Glivec doses in GIST, and he was also taken aback when at a GIST meeting patients presented a study disregarding the 'intent to treat' principle in analysing data. "I said I'd never heard in any medical congress someone challenging the principles of clinical research. However questionable all that could be, I thanked them for their radical thinking, as they don't have the luxury of waiting for survival data at the end of trials. I am thinking now of involving patients in the ESMO recommendations on GIST." A particularly active advocacy group is the US-based Life Raft, which is laying down its own model for allocating GIST research funds, in a similar way to other groups such as the Multiple Myeloma Research Foundation.

Casali has little in the way of distractions outside of work. Indeed, he says that pursuing some of the issues surrounding sarcoma, such as lobbying European decision makers and writing on the clinical method, are his 'hobbies', alongside chess, which he views in much the same light as clinical decision making. "Instead of collecting stamps I look at clinical ethics," he jokes.

He has no immediate plans beyond staying at the Milan unit and his priorities of extending the networks in Italy and Europe, and is not likely to change course from sarcoma and rare disease. But one hopes he will find time to write about the clinical method – in English this time of course.

"I thanked them for their radical thinking, as they don't have the luxury of waiting for survival data"

Controversial issues in managing locally advanced head and neck cancers

Great strides have been made in managing patients with locally advanced squamous cell cancer of the head and neck over the past 20 years. Novel approaches using chemoradiation (CRT) have improved disease control and quality of life. But controversies remain about how to optimise the use of CRT, including the role for targeted therapies, and how best to manage high-risk patients.

Major developments in managing patients with locally advanced squamous cell carcinomas of the head and neck have led, in many clinical settings, to significant advances in treatment efficacy and improvements in disease prognosis. The co-administration of chemotherapy and radiotherapy – chemoradiotherapy – both as definitive and adjuvant treatment, has been shown to be more efficacious than radiotherapy alone. However, recent prospective trials warn that poor tolerability with aggressive approaches impacts on treatment dose intensity, leading to the delivery of sub-optimal regimens.

Tailoring novel, multidisciplinary approaches based on drug–radiation interactions enables clinicians to optimise treatment outcomes in terms of both disease control and quality of life. As therapy becomes more intense, it is essential to monitor treatment-related morbidity as a crucial element in estimating the

European School of Oncology
e-grandround

The European School of Oncology now 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 will be selected for publication in each issue of *Cancer World*.

In this e-grandround, Jacques Bernier, Department of Radio-oncology, Genolier Swiss Medical Network, Genolier, Switzerland, reviews the controversies in managing locally advanced head and neck cancers. His presentation was summarised by Susan Mayor.

The recorded version of this and other e-grandrounds, including the discussion following the presentations, can be accessed at http://tiny.cc/grandround

therapeutic gain from different strategies. The increasing use of longer, more aggressive combined treatments provokes a number of controversies regarding the impact on disease control, both above the clavicle and distantly, and the potential deleterious effect on adherence with radiotherapy and systemic treatment doses.

The focus of this e-grandround is on three main aspects of head and neck oncology: organ preservation, the treatment of unresectable disease and management in the postoperative setting.

Recent data for 2002 show that there were more than 500,000 new cases of squamous cell carcinoma of the head and neck (SCCHN) worldwide, and 300,000 deaths. Of these, just under half (42%) affected the oral cavity as the primary tumour site, one-third (33%) the larynx, and one-quarter (25%) the pharynx. Altogether, these cancers account for approximately 5% of all malignancies worldwide. This excludes cancers of the nasopharynx, which are more frequent in Asian countries.

Studies have demonstrated that chemoradiation (CRT) is more effective than radiotherapy alone in the treatment of locally advanced SCCHN. However, use of CRT is associated with a significant increase in acute toxicity. The maximum tolerable toxicity may have been reached with the dose intensities currently used.

The Meta-analysis of Chemotherapy in Head and Neck Cancer (MACHNC), which is probably the most well-known study in this area, showed that the addition of chemotherapy to radiotherapy achieves benefits in locoregional control and in overall survival. Results showed that concomitant CRT was more effective than use of adjuvant or neoadjuvant treatment with radiotherapy alone, with a gain in survival of 19%, which is highly significant.

Does this mean that CRT should be given to all patients with locally advanced disease? Certainly not, we need to consider the individual patient. A recent substudy showed that age should be taken into account.

Stratifying the gain in overall survival with CRT versus age showed a gradual decrease in benefit between the ages of 50 and 70 years, with a minimal gain for patients aged 70 and older. This is something that should be considered at the time of making treatment decisions, and emphasises the need for individual patient decision-making on a case-by-case basis.

The other side of the coin is toxicity. This was certainly illustrated in a study by Cooper et al., demonstrating that the use of CRT in the postoperative setting results in a significant increase in acute toxicity – both nonhaematological and haematological – compared to radiotherapy alone (*N Engl J Med* 204:1937–44). More than three-quarters (77%) of patients treated with CRT had toxicity of grade 3 or more compared to 34% of those who had radiotherapy alone ($P<0.001$) following surgery. This demonstrates that there is a price to pay for patients given chemotherapy concomitant with radiotherapy.

The main controversies

- Is the therapeutic index for chemoradiation jeopardised by its toxicity?
- Do we know how best to exploit targeted therapies?
- How aggressive should we be with adjuvant treatments?
- Should we use chemoradiation or sequential treatment in high-risk patients?

Too toxic?

Is the therapeutic index for CRT jeopardised by its toxicity? The answer to this question can be gained by looking at three randomised phase III trials, carried out in France, Switzerland and Germany.

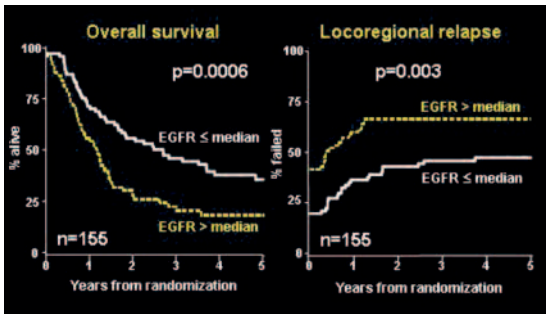
Results showed that use of CRT compromised patients' adherence to chemotherapy, and this loss of adherence increased with the number of chemotherapy cycles. Approximately one-third of all patients did not receive the intended number of chemotherapy cycles (*J Clin Oncol* 22:4665–73, *JNCI* 91:2081–86, *J Clin Oncol* 16:1318–24).

There are two main observations regarding the future of CRT, at least with the drugs currently in use. The first consideration is that the acute toxicity of CRT compromises adherence to chemotherapy and radiotherapy protocols in more than one-third of cases. As a consequence, these patients receive suboptimal doses (or dose intensities) of chemotherapy and/or radiotherapy. The second issue is the late effects of CRT.

A study by Argiris et al. provides valuable information on these issues (*Clin Cancer Res* 10:1956–62). Results from five studies which investigated the role of CRT in locally advanced disease showed that disease progression and comorbidities were the two main causes of death following therapy. However, treatment-related causes were in third position, accounting for 15% of deaths, with 9% being early deaths and 6% late deaths due to complications associated with treatment.

So, both acute and late effects of CRT on normal tissue are a matter of concern. These concerns, together with recent advances in translational research with noncytotoxic agents, have led teams to embark on research along new avenues with targeted therapies.

EGFR: A MARKER FOR RESPONSE



Higher EGFR expression is associated with a higher risk of relapse and poorer survival following radiation therapy
Source: K Ang et al. *Cancer Res* 62:7350–56

ARE TARGETED DRUGS THE ANSWER?

Can we opt for other ways of treating patients that could increase the therapeutic index, using targeted therapies? Research began two decades ago in developing molecular therapies and strategies that act on specific proteins, processes and pathways implicated in cancer. The rationale for the targeted approach is to increase selectivity for tumour cells and reduce toxicity in normal tissues. This discussion will focus on the interaction between radiotherapy and antibodies against epidermal growth factor receptor (EGFR).

EGFR is a member of an important family of transmembrane proteins associated with signalling pathways central to cell growth and differentiation. When a specific ligand binds to the EGFR, the receptor activates a number of signalling pathways, in particular AKT, STAT and MAPK. This results in gene transcription in the cell cycle progression, affecting proliferation/maturation, survival and anti-apoptosis, angiogenesis and invasion/metastasis. Blocking the EGF receptor is likely to affect tumour cell growth and response to treatment.

A lot of things changed after the study a few years ago by Ang et al. (*Cancer Res* 62:7350–56), which showed the predictive value of EGFR expression as a marker for response to radiotherapy. The study demonstrated a strong correlation between EGFR expression and treatment outcome in a subgroup of 155 patients. Whatever the endpoint – overall survival or locogregional relapse, the higher the EGFR expression, the more dismal the progression. How can we exploit this observation to optimise patient treatment?

Among the agents able to inhibit EGFR activation, cetuximab (C225) has been the most investigated so far. Cetuximab is an IgG1 monocolonal antibody that binds specifically to EGF receptors and inhibits endogenous ligand binding, thereby blocking receptor dimerisation; tyrosine kinase phosphorylation and receptor-dependent downstream signalling in the cytosol.

One of the first translational, *in vitro* studies with cetuximab (*Cancer Res* 53:4637–42) demonstrated marked synergy with cisplatin in A431 xenograft growth inhibition. The addition of C225 to cisplatin induced complete inhibition of cell growth. A few years later, a further study demonstrated the same pattern with C225 when added to radiotherapy.

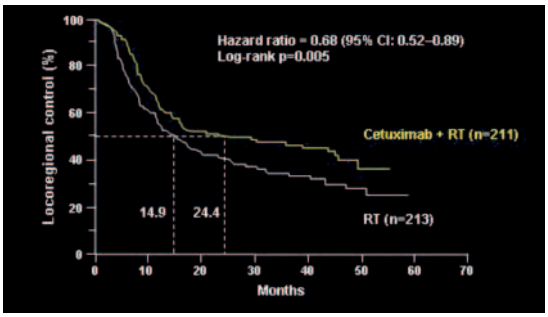
The translational research studies set the stage for prospective clinical investigations with cetuximab plus radiotherapy. A study by Bonner et al. (*N Engl J Med* 354:567–578) assessed radiotherapy plus cetuximab in patients with squamous-cell carcinomas of the head and neck. The majority of the patients presented with pharynx cancer, with the tumours arising mostly from the oropharynx (63%). About one-quarter of the patients had larynx tumours.

Patients were stratified by TNM stages, performance status and radiation schedule. The control arm received radiotherapy alone, either in conventional or accelerated regimens, while the experimental arm was given the same regimen of radiotherapy therapy together with weekly doses of cetuximab, with an initial dose just before the start of radiotherapy. The study accrued 424 patients.

The main endpoint was locoregional control. This increased from a median of 14.9 months to 24.4 months with cetuximab (log rank P=0.005). The locoregional control rate at three years was 13% higher in favour of the cetuximab arm (47% vs 34%), which was highly significant (P<0.01). The same pattern was seen for overall survival, with a difference of almost 20 months for the combined modality over radiation alone, and a survival rate difference of 10% at three years (55% vs 45%; P=0.05).

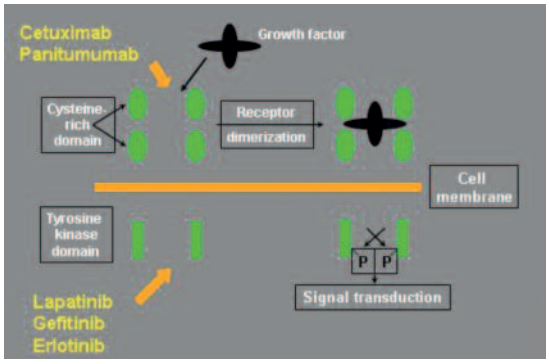
The safety profile is worth revisiting. There was no difference in radiation-

BENEFIT OF CETUXIMAB



Adding the EGFR inhibitor cetuximab to radiotherapy improves locoregional control
Source: J Bonner et al. *N Engl J Med* 354:567–578

HOW EGFR INHIBITORS WORK



EGFR is a protein associated with signalling pathways central to cell growth and differentiation. Blocking the EGF receptor is likely to affect tumour cell growth and response to treatment

induced toxicity when cetuximab was added to radiotherapy. As expected, the only difference observed was an acne-like rash, which was observed in 17% of the patients with grade 3–5 side-effects treated with cetuximab, compared to only 1% of those given radiotherapy alone. Infusion-related reactions were seen in only 3% of the cetuximab-treated group, due to a hypersensitivity to the infusion.

How does chemoradiation compare with cetuximab plus radiotherapy? As discussed previously, three trials showed a significant decrease in adherence to CRT, with two-thirds of patients able to complete two cycles of chemotherapy. Bonner demonstrated adherence of about 90% with cetuximab plus radiotherapy, so it seems that adherence is better with a protocol based on targeted therapy.

A survival advantage has been demonstrated with both modalities. Four trials of CRT showed a median survival advantage of 7–18 months, while the survival advantage in the Bonner trial was 20 months.

Targeted therapies certainly work in head and neck cancer, and there are now several options. First, there are agents that act on the outer domain of the EGFR, including cetuximab and panitumumab. Second, there are the small molecules, such as lapatinib, gefitinib and erlotinib, which inhibit the tyrosine kinase domain at the first level of the phosphorylation mechanism.

The Bonner trial demonstrated that cetuximab plus radiotherapy is more efficacious than radiotherapy alone. It compares favourably with CRT in terms of efficacy and is less toxic. Several ongoing studies are investigating the role of CRT plus cetuximab.

Selecting patients

Should chemotherapy be added to radiotherapy in all high-risk patients? To try to answer this question, it is useful to go back to the design of the EORTC 22931 study, which was conducted in the 1990s. After primary surgery, patients were randomised to receive either postoperative radiation therapy with a conventional regimen or to postoperative radiotherapy with the same regimen plus chemotherapy with cisplatin (DDP) at a dose of 100 mg/m^2 on days 1, 22 and 43.

One of the most striking results was the increase in overall survival with CRT. The Kaplan Meier curves showed a significant increase with CRT, with a difference of 13% in overall survival at five years (P=0.01).

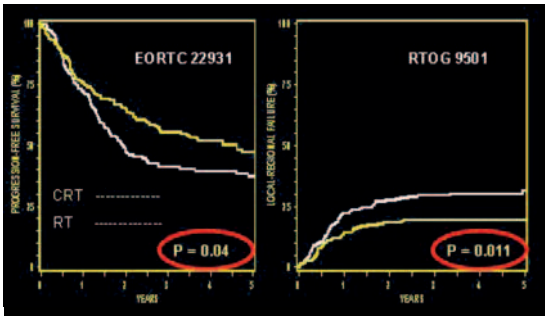
At the same time, the RTOG team (Radiation Therapy Oncology Group) conducted a similar trial with the same design, also in patients presenting with locally advanced disease. The primary endpoints in both studies – progression-free survival in the EORTC study, and local-regional failure in the RTOG study – showed that CRT was superior to radiotherapy alone.

What is noteworthy in these trials is that, when we deal with locally advanced disease, the selection criteria can be very different from one study to another. In the EORTC study, stage III-IV disease, oropharynx or oral cavity tumours with level 4 or 5 lymph nodes, perineural disease and vascular embolisms were considered high-risk factors.

In contrast, the RTOG study identified two or more positive nodes as indicating high risk. The two studies identified only two high-risk factors in common – positive margins and extracapsular effraction (ECE). These two risk factors were associated with significantly poorer overall survival than the other risk factors in both studies.

Comparing the effect of chemotherapy in the two trials, there was a trend in favour of chemotherapy for patients without positive margins or ECE in the EORTC trial, but the RTOG study ▶▶

BENEFIT OF CHEMORADIATION



The two major trials showed better outcomes for chemoradiation compared with radiotherapy alone in both locoregional control and progression-free survival

Sources: J Bernier et al. *N Engl J Med* 350:1945–52; JS Cooper et al. *N Engl J Med* 350:1937–44

Ahmad Awada (AA), from the Institut Jules Bordet, Brussels, put questions to Jacques Bernier (JB) about the controversies surrounding CRT in head and neck cancers

AA: *Do we need a study to compare chemoradiation directly with radiotherapy plus cetuximab?*

JB: There is no direct and randomised comparison between radiotherapy plus targeted therapies versus CRT. This should be addressed. In terms of the recent past, it is useful to compare the study from Bonner demonstrating high efficacy and low acute toxicity (it is still a bit early to see late toxicity) with another study of CRT. Historical comparison shows the efficacy of cetuximab plus radiotherapy compares favourably with CRT and is less toxic – but there is no direct comparison.

AA: *It is not clear what effect radiotherapy plus cetuximab might have on distant metastases – this is still a problem with concurrent chemotherapy and radiotherapy.*

JB: CRT trials – both individual studies and intergroup studies – show it is very difficult to elicit benefit in terms of reduction of distant metastases with standard CRT. One study showed a small benefit in terms of the pool of CRT trials, but this is difficult to demonstrate on a large scale. We need other solutions to reduce distant metastases beyond the concept of CRT.

There are three options: a trial with induction chemotherapy – this is probably one solution, especially with taxotere plus cisplatin and 5-FU. The second option is to wait for results from sequential treatment – induction chemotherapy then CRT – looking at distant metastases and toxicity. The third option, as in EXTREME, is to include a maintenance trial with cetuximab or other targeted therapies in the long term. We observed survival benefit in EXTREME.

A combination of induction chemotherapy plus targeted therapy could be of interest to improve response rate. The EXTREME study showed improved survival and response rate. We have to wait for results from two EORTC studies.

AA: *In locally advanced stage III and IV head and neck cancers, there are now several strategies based on clinical trials. We have induction therapy followed by CRT and radiotherapy plus targeted therapy. I think we are in a better position to choose the optimal therapy for each patient.*

JB: I agree. There is preparatory work to be done before deciding how to treat an individual patient. One aspect is to check the risk level – don't treat intermediate-risk patients in the same way as high-risk patients. Second, check the patient's general condition to assess whether he is sufficiently fit for chemotherapy. Third, check whether you are embarking on an organ preservation programme – whether you are aiming to keep a functional organ, e.g. the larynx, in place. Delayed toxicity must also be taken into consideration. Check all this before making a decision.

It is clear that, for low- and intermediate-risk patients, the toxicity of chemotherapy in combination with radiotherapy is not justified, so we need other solutions. From Bonner, targeted therapy plus radiotherapy is one solution. Hyperfractionation, or altered fractionation, can be used, with or without targeted therapy.

In very-high-risk patients, treatment depends on the general condition of the patient. There are probably two options. Induction chemotherapy can be used first in very bulky disease, difficult to irradiate disease, or patients at high risk and with distant metastases or bulky disease in the hypopharynx. An extreme risk level justifies differences in therapeutic approach.

AA: *It is important to look at comorbidities. The aim of organ preservation and life expectancy could influence choice of therapy. The Bonner study told us that a combination of radiotherapy plus cetuximab may be useful in patients with renal problems – chemotherapy is difficult in this group. This combination is useful because you could not give cisplatin. It also seems from the presentation that CRT is not really favoured in elderly patients. Here, might radiotherapy plus cetuximab be of interest?*

JB: The effect of chemotherapy decreases with age; this is also found with hyperfractionation and altered fractionation without chemotherapy. With or without chemotherapy, there is a decrease in effect with age, probably due to dose intensity with radiotherapy alone or radiotherapy plus chemotherapy not having a very positive effect above the age of 70. There is definitely a place for other solutions – a test use of targeted therapy plus radiotherapy in a subset with a lot of comorbidities is fully justified.

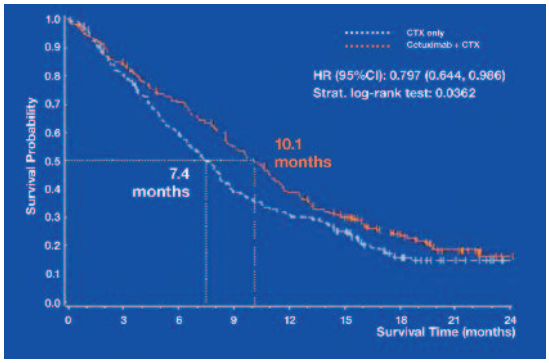
AA: *Any contraindication to cetuximab with antabuse (disulfiram)? To my knowledge, there is no information on this.*

JB: I have not seen any notification on potential interaction between the two compounds.

AA: *Is there any role for electroporation therapy [designed to increase uptake of a therapeutic agent into the cell interior] in combination with targeted therapy?*

JB: No, it may apply for some oral cavity or oropharynx tumours, as it is quite active but quite toxic to the mucosa. It is still experimental, with no large-scale study. The toxicity of this method is rather high, so to combine it with other toxic drugs could be a problem. Images I have seen after electroporation suggest that you should use it with caution, but it could be very efficient for small lesions.

IMPACT ON METASTATIC DISEASE



Last year, the EXTREME trial demonstrated an increase in overall survival in patients with advanced disease from 7.4 to 10.1 months by adding cetuximab as a maintenance therapy to chemotherapy – this was the first increase in 20 years
Source: J Vermorken, presentation at ASCO 2007

demonstrated no effect of the addition of chemotherapy.

In terms of the postoperative setting, differences in selection criteria explain variations in the impact of chemotherapy. High-risk patients derive a benefit from CRT compared to radiation alone in the postoperative setting. Adjuvant CRT and radiotherapy are particularly indicated for patients with positive surgical margins and those with ECE in neck nodes.

CRT OR SEQUENTIAL TREATMENT?

The use of chemotherapy followed by radiotherapy was investigated 15 years ago, when an EORTC study compared it to primary surgery. More recently, two trials, one in Europe and one in the US, investigated the impact of the addition of docetaxel and cisplatin and 5-FU.

The EORTC study 24971 included patients with unresectable SCCHN, who were treated with four cycles of induction chemotherapy with PF (cisplatin plus 5-FU) as standard treatment, with the addition of docetaxel in the experimental arm. This trial demonstrated significant benefit in terms of overall survival in patients treated with docetaxel plus cisplatin and 5-FU (TPF).

Several institutions have been investigating the use of sequential treatments, for which the rationale is:

1. to decrease numbers of failures above the clavicle, which is bound to result from high response rates and enhanced complete response rates prior to CRT;

2. to reduce the incidence of distant metastases, which is bound to result from the use of full doses of chemotherapy, especially during the induction phase.

Sequential treatment studies have used different regimens of induction chemotherapy, such as PF/TPF every three weeks x 3, or carboplatin/paclitaxel (C/P) every three weeks x 2, followed by concomitant CRT.

Use of a sequential treatment strategy has two main challenges. First, to achieve the objectives of fewer local and distant failures, sequential treatments must use aggressive induction therapy, which should not compromise the CRT dose intensity. Second, the integration of induction chemotherapy and CRT is likely to cause problems of tolerability, resulting in suboptimal treatment delivery, increased toxicity and reduced quality of life.

THE EXTREME TRIAL

It is worth mentioning a trial conducted in another setting (patients with recurrent/metastatic SCCHN), which could provide new insight regarding the impact of systemic treatments on metastatic disease.

The EXTREME trial compared chemotherapy with carboplatin or cisplatin and 5-FU versus the same regimen to which cetuximab was added. In the cetuximab arm, cetuximab was continued as maintenance therapy after a maximum of six chemotherapy cycles and compared to no maintenance treatment in the standard treatment arm.

Results, presented at ASCO in 2007, showed an increase in overall survival – for the first time in 20 years – from 7.4 to 10.1 months. This gives new insight, showing what we could expect from maintenance treatment, with a positive impact on distant metastases, which remain a growing problem with the improvements in locoregional control of locally advanced disease.

CONCLUSIONS

The high levels of toxicity associated with chemotherapy are not justified in patients with low rates of failure above the clavicle. The main options are:

- Radiotherapy plus targeted therapies (EGFR inhibitors, VEGF inhibitors etc)
- Definitive radiotherapy, with altered fractionation
- In the postoperative setting, the use of molecular markers as prognostic indicators for treatment outcome

In high-risk patients, chemoradiation is more efficacious than radiotherapy alone, but is more toxic. At the moment, there has been no direct comparison between chemoradiation and radiotherapy plus targeted therapies.

Current approaches might be improved by increasing local control obtained by radiotherapy through use of novel cytostatic agents, combining cytotoxic and non-cytotoxic agents and use of peri-operative chemotherapy in the adjuvant setting.

Options to reduce the risk of distant metastases include novel multidrug regimens and maintenance treatment with chemotherapy or targeted agents.

When is it OK to randomise cancer patients to placebo?

Anna Wagstaff

No-one wants to see progress in cancer research more than the patients themselves. But how do we deal with potential conflicts of interest when testing new drugs involves giving placebos to people dying of cancer?

Karen has incurable GIST. She has been kept alive for four years thanks largely to Glivec (imatinib), but eventually developed resistance and was put on Sutent (sunitinib), which kept the tumour in check for a further year. Her latest CT scan, however, reveals that the disease is progressing and she is pinning her hopes on a new drug being trialled for people like her who have run out of options.

The new generation of targeted drugs has certainly transformed the outlook for GIST patients – and she is keen to give it a go. But her only option is the lottery of a phase III randomised trial, where she stands a 33% chance of being given a substance designed to have no deterrent effect at all on the tumour that is killing her.

This will be a crossover trial, and Karen has been assured that if she is in the placebo arm, she will be allowed to change to the active drug – a treatment that is not available outside a clinical trial – if her disease shows signs of progressing. She will be checked every six weeks – twice as often as she is checked outside the trial.

She thinks it very likely that waiting until her cancer has progressed before getting the active treatment means she will die earlier than if she started on the active treatment straight away. But she also knows that, until the trial is done, it is impossible to say whether this is the case, or how many weeks, months or years she would stand to lose. The phase II trial had shown marked, not dramatic, activity – so it is clearly no wonderdrug. But the fact that the company has decided to invest in a phase III trial indicates some confidence that it will show sufficient benefit to stand a fair chance of approval.

Karen would like to try the drug. She appreciates that the trial at least guarantees her better supportive care and understands that progress in cancer medicine depends on being able to show that experimental treatments show meaningful clinical benefit. But she still does not like the one in three chance that she would be randomised to a placebo.

Despite being told that, on the active arm, serious side-effects could outweigh any potential benefit, she remains convinced that her best bet is to get that drug before her disease progresses further. She decides to wait for an expanded access programme somewhere or to apply to join a phase II trial if she can find one. The phase III trial, she thinks, will have to find some other patient to randomise.

Progress derailed?

Karen is a hypothetical patient, but her dilemma is real enough. The reluctance of many patients in her position to join randomised placebo-controlled trials is creating concern among many researchers, who argue that this trial design – used rarely in cancer over past decades – is becoming an increasingly vital option for getting the new generation of cytostatic drugs to market. Whereas cytotoxics shrink tumours, cytostatic therapies aim to merely control the disease – and proving a cancer is not progressing can be quite tricky.

For instance, though cancers are rarely known to shrink of their own accord, it is not uncommon to go through periods of remission where growth slows or stops for a while. Without a placebo comparator arm, it can be hard for the researchers – and regulators – to distinguish the effect of the drug from the natural history of the disease.

The assessment of whether a patient's disease has progressed or remained stable is also seen as a problem, being considered to be more susceptible to investigator bias than measurements of tumour shrinkage. Using a double-blind placebo-control design (where neither patients nor clinicians know which patients are in which

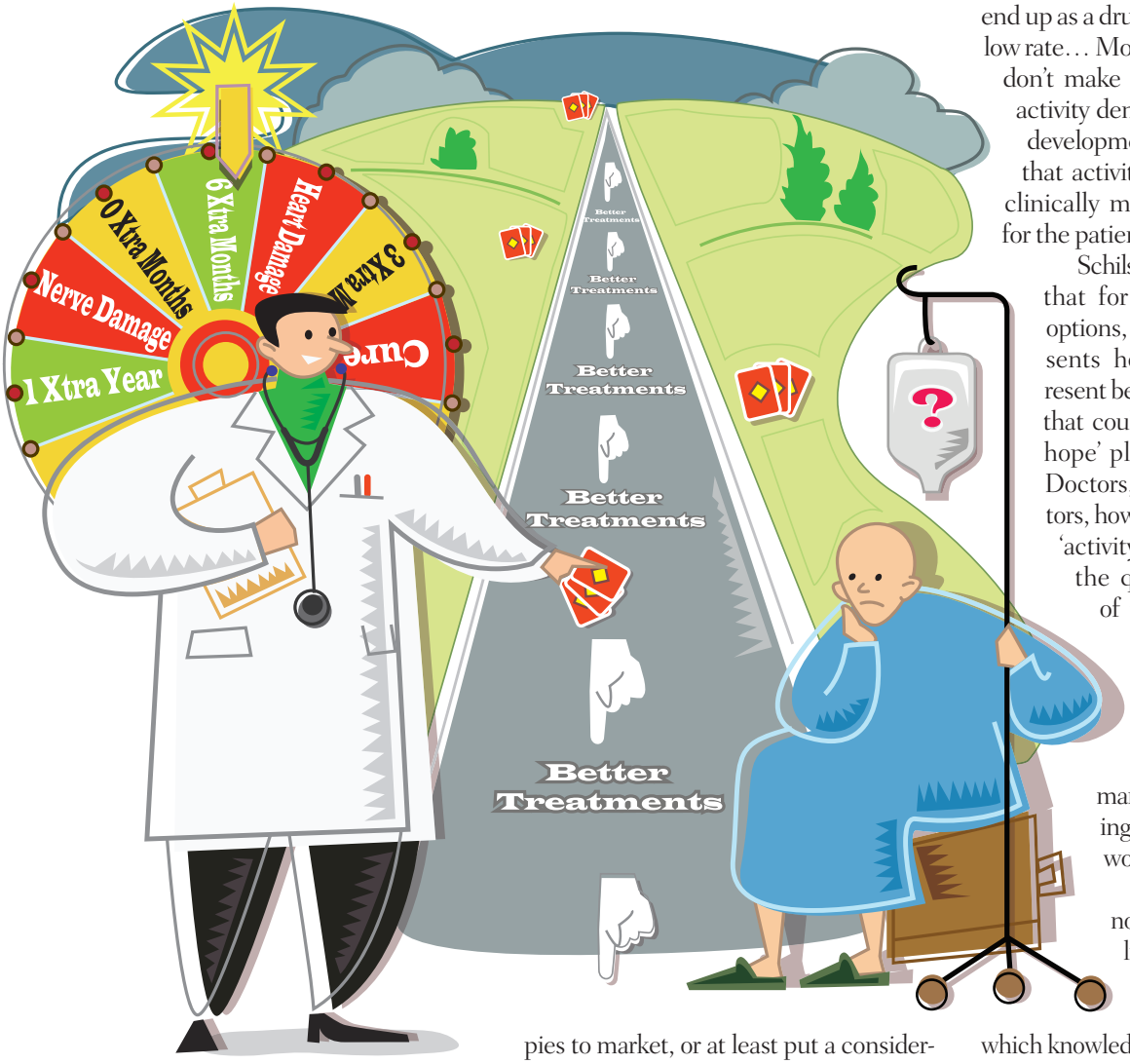


ILLUSTRATION: FRED VAN DEELEN, WWW.ORGANISART.CO.UK

arm) can be important in convincing the regulators that over-enthusiastic clinicians have not read more into the efficacy of their experimental drug than it merits.

The concern is that if patients are unwilling to participate in trials with placebo arms, they could jeopardise the chances of getting promising new therapies to market, or at least put a considerable brake on progress.

Richard Schilsky, professor of medicine at the University of Chicago, is actively highlighting these concerns. "If you look at the success rate over the last 10 years or so of getting new oncology drugs approved, only 5% of new oncology drugs that enter clinical testing actually make it through phase III testing and end up as a drug approval. It is a dismally low rate… Most of the 95% of drugs that don't make it through phase III had activity demonstrated earlier in their development, but most of the time that activity does not translate into clinically meaningful improvements for the patients."

Schilsky understands completely that for patients with no other options, evidence of activity represents hope, and these patients resent being obliged to join a lottery that could randomise them to 'no hope' plus best supportive care. Doctors, researchers and regulators, however, need proof that such 'activity' could actually improve the quality of life or survival of their patients – and that could require a placebo-controlled randomised clinical trial. Without that, all sorts of compounds could enter the market without anyone having any real idea about what works and what doesn't.

Many patients who have now reached the end of the line, says Schilsky, have benefited earlier in their disease from therapies about which knowledge was gained thanks to an earlier generation of patients who agreed to subject themselves to the lottery of a randomised controlled trial.

Framing the discussion

Earlier this year, Schilsky teamed up with a group of oncologists, trialists, regulators and ethicists to write a position paper, on behalf of ASCO, on the Ethical, Scientific,

If patients are unwilling to participate in trials with placebo arms, they could put a brake on progress

and Regulatory Perspectives Regarding the Use of Placebos in Cancer Clinical Trials (*JCO* 26:1371–78).

The paper argued that there is an ethical case for randomising cancer patients to different treatment arms (either a head-to-head comparison of active treatments or active treatment versus placebo), when there is "genuine uncertainty or disagreement about the relative merits of two or more therapies within the expert medical community" – a situation they refer to as 'clinical equipoise'. One important corollary of this is that "participants should not receive a treatment inferior to what is otherwise available in clinical practice" – which rules out the use of a placebo arm where an established effective treatment exists for that group of patients.

The issue of whether it is ethically acceptable to randomise some trial patients to placebo then rests on whether a placebo arm is really necessary in order to obtain reliable data – methodological criteria – and whether the patients on the placebo arm would be put at unacceptable risk – ethical criteria.

The ASCO paper argues that placebo controls may be justified when they are necessary to prove that a new treatment has efficacy:

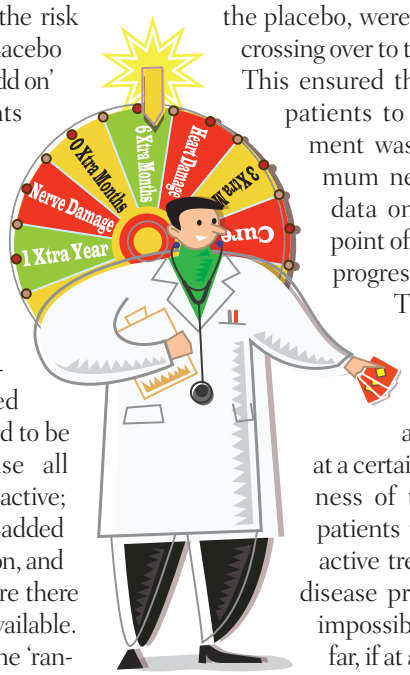
- in a disease with a high placebo response rate, or
- in a condition that waxes and wanes in severity, or has spontaneous remissions, or has an uncertain and unpredictable course, or
- when therapies exist that are only minimally effective or have serious adverse effects, or
- in the absence of any effective therapy.

It adds that there may be a justification for a placebo arm, "to assure that physicians and patients are blinded to treatment assignment so as to minimize bias in assessment of study end points."

However, any such trial would have to be designed in such a way that, "a patient randomly assigned to placebo should not be substantially more likely than those in active treatment group(s) to die; suffer irreversible morbidity, disability, or other substantial harms; suffer reversible but serious harm; or suffer severe discomfort."

Mitigating trial designs

The paper looks at trial design options that could help minimise the risk posed to patients on the placebo arm. Key among these are 'add on' designs, where all patients receive an established active therapy, but are then randomised to receive, in addition, either the active experimental drug or placebo. Many new targeted therapies have been tested in this way in combination with an established cytotoxic. Such designs tend to be less controversial because all patients receive something active; however, they introduce an added complexity of drug interaction, and they are not an option where there are no effective therapies available.



Another possibility is the 'randomised discontinuation design', as used in the phase II trials of sorafenib (Nexavar) for kidney cancer, in which a placebo arm was used because there was no pre-existing therapy. All trial patients were offered the active therapy to start with, and those who clearly responded were kept on it. Those who progressed or experienced serious toxicity were taken off it. Only those in the middle who tolerated the drug and showed stable disease, so that the benefit/toxicity balance was unclear, were randomised between the active drug and placebo. This allowed the trial to go ahead while guaranteeing access to patients who clearly benefited from the drug and sparing needless suffering to those who clearly did not.

Then there is the crossover design, as used in the phase III trial of sunitinib for GIST patients who had become resistant to Glivec, when the absence of pre-existing further lines of therapy was seen to justify a placebo arm. Patients were randomised 2:1 between sunitinib and placebo, and were closely monitored. Those showing progressive disease were then unblinded, and if it turned out that they had been on the placebo, were given the option of crossing over to the active treatment. This ensured that the exposure of patients to the inactive treatment was kept to the minimum necessary to provide data on the primary endpoint of the trial, which was progression-free survival.

These trial designs go a long way towards making placebo controls more acceptable, although at a certain cost to the robustness of the data. Allowing patients to cross over to the active treatment on signs of disease progression makes it impossible to find out how far, if at all, the experimental drug increases survival. And while improved progression-free survival (PFS) has been shown to correlate with improved survival in some cases, that does not mean that this can be assumed for all drugs in all disease settings.

The ASCO position paper was intended to add some clarity to the discussion about the use of placebos, to assuage concerns and to contribute to increased enrolment in clinical trials. How far it has fulfilled its aims is difficult to tell as, much to Schilsky's surprise, the paper seems to have sparked little controversy.

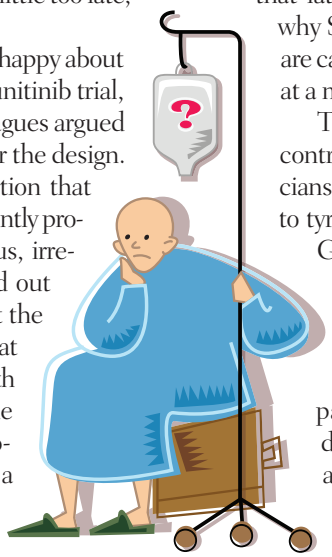
Who decides?

One patient advocate whose concerns have certainly not been assuaged is Norman Scherzer, executive director of the US GIST patient organisation Life Raft. With regard

to the criteria presented in the ASCO paper to justify placebo-controlled trials, he poses this question: who decides? Who decides that such a trial design is necessary on this or that methodological criterion? And who decides that the patients exposed to placebo are not placed at an unacceptable risk?

"If you propose giving a placebo to terminally ill patients to demonstrate that their disease progression or death rate will be greater if they are not given the drug, you must assume the burden of demonstrating that there are no alternatives, and that patients on the placebo arm really won't suffer serious irreversible harm," says Scherzer. "Secondly, you must include the recipients of the placebo in the decision-making process. Not in the consent process down the line, which is too little too late, but in the process itself."

Life Raft was deeply unhappy about the use of placebo in the sunitinib trial, and Scherzer and his colleagues argued hard for the sponsor to alter the design. They challenged the assertion that the crossover design sufficiently protected patients from serious, irreversible harm. "We worked out some theoretical models at the time where we showed that the amount of tumour growth one could experience while on a placebo was pretty substantial. Because you had a combination of the wash-out period [where all trial patients come off their previous medication to clear the system] and then the time that it took before you were unblinded. Also they defined the tumour progression by a standard – RECIST – that much of the clinical community has rejected, which requires a measurement that allows tumours to grow well over 20% before you are considered actually progressing."



Life Raft asked the sponsors to consider some alternatives, including the use of an 'historical' arm as a comparator in place of a prospective placebo arm. Relevant data could have been gathered from Life Raft's own data base, in which hundreds of GIST patients voluntarily submit reports of how their disease is progressing, as well as other registries such as that of the US Armed Forces Institute of Pathology, argued Life Raft.

Scherzer feels, however, that they were never taken very seriously. No surprise, perhaps, considering how hard it would have been to change a planned trial design at that late stage – which is exactly why Scherzer and his colleagues are calling for patients to get a say at a much earlier stage.

The sunitinib trial was also controversial among many clinicians, who argued that resistance to tyrosine kinase inhibitors like Glivec tends not to be absolute: some tumour cells still respond. They argued that, in the absence of anything better, trial patients should be randomised between sunitinib and remaining on Glivec, but it turned out to be impossible to have a meaningful dialogue with the sponsor.

Peter Reichardt, a GIST specialist from the Helios Kliniken in Bad Saarow, Germany, found the experience very frustrating. "The sponsor will say that the regulators require this design, and if we don't use this design they will not accept the results. You either accept it or you don't participate in the trial. So the clinicians then have to go to their patients and say: we have no room to argue, so you either join the trial with a 33% chance of getting a placebo, or you don't."

Scherzer doubts that the regulators really did insist on a placebo design. "On occasions when we went back to the FDA, it turned out not to be the case. The FDA expects the industry to meet certain scientific standards of proof. In no trial does the FDA tell a company in advance what they need to build into their protocol.

"A placebo is certainly a very viable standard of proof. It clearly helps to demonstrate something, and might help to do so more efficiently in terms of time and cost than not using a placebo. But that wasn't the question. The question was: was there an alternative?"

Had Glivec been used instead of placebo, he adds, one might have expected to see a smaller difference between the two arms, and it might have taken more patients, more time and more money to reach the standard of proof required by the regulator. "Is that an acceptable reason for exposing a certain number of patients to a placebo? We would say no.

"We would also argue that using the current standard of treatment – in this case Glivec – in place of a placebo is better science, for what we are interested in is not whether a new drug is better than nothing, but whether it is better than the current standard of treatment."

No room for manoeuvre

Thierry Le Chevalier, who heads GSK's Oncology Clinical Development in Europe, says that the major problem is the complexity involved in getting a drug to

Who decides that the patients exposed to placebo are not placed at an unacceptable risk?

"When you leave out the guinea-pig – in this case the patient – I do think that is by its nature somewhat unfair"

market under different regulatory regimes, which leaves very little room for manoeuvre. "In big companies you don't work only with Europe, you have to work with the US, Japan, Korea etc… and they all have different standards of proof and registration. For instance, when you speak to EMEA you cannot make any decision that interferes with what is required by the FDA."

As well as meeting different standards for measuring efficacy, companies have to meet different safety standards and manufacturing requirements for consistency and shelf-life. All this has to be dealt with in parallel, so that the company can manufacture the drug as soon as approval is given. Upsetting one part of the equation could derail a process that has taken years.

Le Chevalier came to GSK from a career spent largely at France's Institut Gustave Roussy. He shares the French enthusiasm for giving cancer patients access to experimental drugs as early as possible, and feels uncomfortable about offering placebos to any patient in a phase III trial in his clinics.

"In a phase II one is looking for activity, so it generally easy to obtain consent from a patient to participate. But in phase III studies you know there is the potential for a substantial response. Everyone knows going to phase III sends out strong signals of confidence in the drug. And if the patient knows he has only a 50% chance to get that drug – that is just frustrating." It is doubly frustrating, he says, for patients who have run out of options – one good reason, he adds, for trialling drugs in earlier disease settings where possible.

"What I would say is that, if the placebo is acceptable and unavoidable, it is mandatory to have very strong early stopping rules... Sometimes you see differences that are extremely significant from a statistical point of view, and you can imagine that the same results might have been visible with fewer patients."

Whether the difference is big or small, Le Chevalier accepts that the control arm of any randomised trial is in some sense 'supposed' to perform worse in order to prove the activity of the investigational product, and when that trial design involves giving a placebo to a cancer patient with no other options, this is not a comfortable thing to do, even if you are convinced it is the only way to get a potentially important new drug on to the market. "For me it is an unresolved problem. If I had the solution to this, I would tell you."

A conflict of interests

Scherzer puts it this way: "We find ourselves comparing the needs of those who are exposed to a placebo against those who might benefit in the future. We agree with ethicists who state that you've got to look at it in the present tense. Good outcomes, no matter how noble, cannot justify research that fails to protect the health and safety of those who participate, particularly terminally ill patients who may have no access to other treatments. When the pathway to a new drug is to run a gauntlet of placebos, that cannot be taken to be consent freely and fairly given. It is coercion by any other name."

Reichardt puts it this way: "If patients argue 'we don't want a placebo trial,' this could result in the trial not happening… Patients have to understand that no trial means no further improvements, no new treatments, no future achievement."

Given the element of conflict of interests in this situation, it might be argued that the only ethical way to proceed would be to allow the patients some say in the way that phase III trials are designed.

This is something Reichardt strongly advocates. "Once a new treatment has shown activity in an early trial, then we can sit down and discuss how can we bring this drug further. Then we start by asking: What kind of trial would be needed to prove efficacy? What would be the target population? What would be acceptable to the regulators? What would be practical with respect to numbers? What would be acceptable to sponsors in terms of money? What would be acceptable to patients as potential candidates for the trial? At that moment the voice of the patient groups could be necessary.

"They can bring their arguments, and learn what it means if they say 'we cannot accept this', and we will say, 'OK then we cannot do the trial', and then they would say 'we want the trial'. And then we can start discussing how to go about this."

The suggestion provokes a certain nervousness among many sponsors, who fear that patient groups could end up holding a gun to their heads. Yet far more damage is already being done by some patient communities who effectively sabotage trials they don't like, by refusing to enrol.

There has to be a better way. "Nobody has a greater interest in fast-tracking testing and approval of new drugs than a cancer patient has," says Scherzer. "The whole process would ultimately be a better process if patients like us were seriously engaged in the decision-making process from the very beginning. We might help come up with a protocol that everybody could live with. When you leave out the guinea-pig – in this case the patient – I do think that is by its nature somewhat unfair."

A reverence for life in turbulent times

Janet Fricker

A young child in wartime Germany, **Stephan Tanneberger** grew up to take a lead in oncology in the communist East, which achieved some of the lowest cancer mortality rates in Europe. His career was cut short after reunification, but Germany's loss proved a gain to the developing world, and to Italy, where he still works ensuring that patients are able to die at home and in dignity.

Grand themes of war and peace dominate the life and work of Stephan Tanneberger, the oncologist who first made his name running a world-class cancer institute in East Berlin, before reinventing himself, following reunification, as a palliative care specialist in Italy. Welcoming the opportunity to reflect back on a life dominated by the major historical events of the 20th century – World War II, the Cold War, the fall of the Berlin Wall – Tanneberger explains how his traumatic childhood experiences, where hunger was an everyday occurrence, hardened his resolve to seek both global peace and a peaceful end of life for patients.

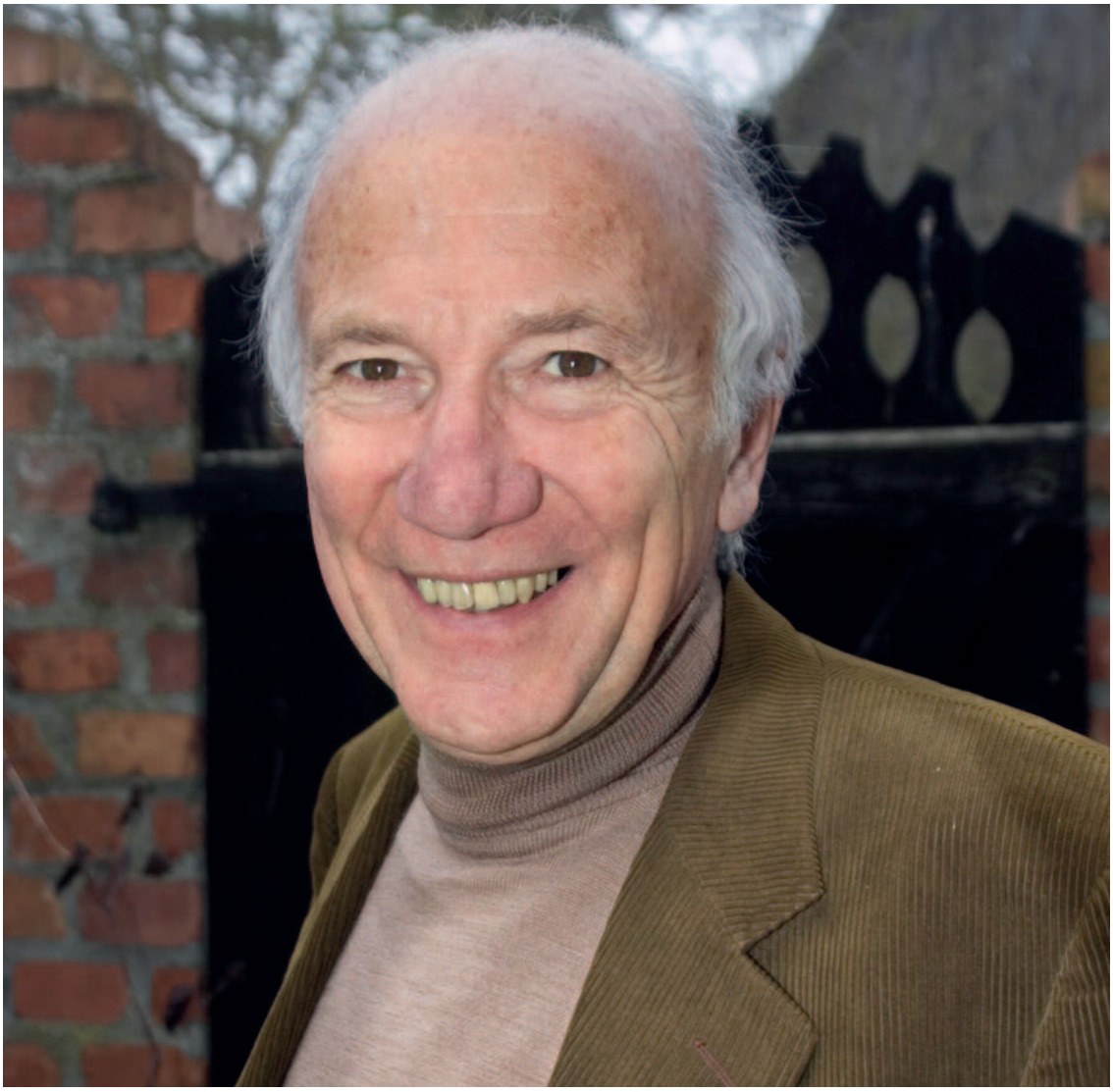
Born in 1935 in Chemnitz, an industrial city in Saxony, Tanneberger was just three when Germany invaded Poland. At first, his family were little affected by world events. "Everyone saw the war in a positive light – it made Germany appear more powerful. As children we were excited by the chocolate sent home by soldiers victorious in Netherlands and France. But I remember unsettling glimpses of Jewish children wearing the yellow Star of David on the streets, and my mother's distress at being powerless to help them."

It wasn't until the prolonged siege of Stalingrad, in 1942, that most Germans became aware of the reality of war. "It represented a change in our perceptions. I witnessed the raw grief of my mother's friends who lost sons," said Tanneberger.

Tanneberger's father Erich, a 42-year-old town hall official who had joined the Nazi party in 1938 as a condition of keeping his job, was called up to protect supply trains travelling to the Eastern front. That same year, allied bombing of Chemnitz started in earnest. "I've still got vivid memories of sitting enfolded in my mother's arms, listening to bombs exploding round us, wondering whether we'd be next." The pattern of their normal existence broke down; days were spent catching up on sleep instead of attending school.

On March 5 1945, in operation Thunderclap, Chemnitz was attacked by 233 US and 760 British aircraft, razing the city to the ground. Their apartment building took a direct hit. Realising it was futile, the family abandoned attempts to fight the fires, and salvaged their possessions.

"Mother kept her head, taking only items necessary to keep us alive – bedding and small valuables



we could sell for food. My 14-year-old brother Konrad worked like a hero against the disaster of that night."

There was no electricity or running water, and they were forced to lead a hand-to-mouth existence, sheltering in bombed out buildings until friends gave them accommodation in a garage. Days were spent scavenging for food and water – and trying to conserve their energy. "My mother pawned her rings to buy bread, but night after night we'd go to bed hungry. Our main goal was to survive," said Tanneberger, remembering how his mother sacrificed her own rations for her children. "The fact we survived is a tribute to her love. She was a wonderful woman."

Eventually, the family were billeted in Niederwiesa, a small village outside Chemnitz. There, Tanneberger remembers the joy of having a permanent roof over their heads, and the surprising kindness of the occupying Russian troops, who gave the children bread and let them ride their ponies.

School resumed in September 1945, bringing a semblance of normality, though food shortages continued. "Although hungry we were energised and full of hope. There was a real desire to work for a better world," says Tanneberger, who seems to

have been remarkably mature for a 10-year-old. "I worked really hard at school because I saw this as my route to becoming a professional, realising early on that getting a job was the best way of helping my mother." As a school student, he excelled at science, and spent spare time playing football and competing in athletics events .

It wasn't until 1946 that his father came home again, released from a prisoner of war camp. "For 18 months we hadn't known whether my father was dead or alive. He returned an old man, totally malnourished, with bad oedema in his legs."

As a former member of the Nazi party, the only employment open for him was back-breaking labour mining uranium in the mountains south of Chemnitz, so Erich was again forced to spend long periods away from his family, this time to earn the money to enable them to buy food. "World events robbed me of a childhood with my father. Between 1941 and 1951 he was away from home and completely out of my life," says Tanneberger.

Ward round at East Berlin's Robert Rössle Institute. Tanneberger became director of this prestigious cancer centre at the tender age of 38

Reverence for life

In 1954 Tanneberger enrolled at Karl Marx University of Leipzig to study chemistry. Inspired by the writings of Nobel Peace Prize winner Albert Schweitzer – a priest turned doctor who expressed his philosophy on the 'reverence for life' through founding a hospital in French Equatorial Africa – Tanneberger determined to study medicine after completing his chemistry degree in 1958. His decision was warmly supported by his professors Eberhard Leibnitz and Ullrich Behrens.

He paid his way through medical school with a job in the pharmaceutical company which was financing labs in the chemical institute of the Academy of Sciences. For years he followed a punishing schedule, working for the company between 7 am and 9 am, then off to medical school between 9 am and 4 pm, returning to do an eight-hour shift at the company between 4 pm and midnight. "I was perpetually on my bike, pedalling furiously between the two centres," he remembers, nostalgically.

Graduating in 1964 with a medical degree and a PhD, he saw oncology as the perfect way to combine his basic science background and humanitarian interests. He started work at the renowned Robert Rössle Clinic in Berlin (the cancer centre of the Academy of Sciences), gaining experience in treating cancer patients, and taking qualifications in internal medicine.

Unused to the concept of free time, he spent his evenings in the lab, researching chemotherapy – a rapidly developing field stimulated by the discovery that cancer could be treated through the therapeu-

He had the idea of 'individualising' treatment using only the drugs most effective in that patient

"Every day we had to think creatively about how to get hold of new drugs, equipment and staff"

tic application of chemical warfare agents. Aware that chemotherapy did not work in all patients and that combining these highly toxic drugs could be very dangerous – and decades before his time – Tanneberger had idea of 'individualising' treatment using only the drugs most effective in that patient. He took cancer cells from individual patients and exposed them to a variety of chemotherapy drugs in the test tube to see which proved most effective. The group performed clinical trials to see if their predictions had clinical relevance.

Although ultimately let down by primitive methodology, Tanneberger published a number of ground-breaking papers, and brought the concept into the public arena. The prognostic assays now on the market and targeted chemotherapy vindicate his early ideas.

A leadership role

Burning the candle at both ends brought Tanneberger to the attention of Hans Gummel, a distinguished cancer surgeon and director of the Robert Rössle Clinic. Late one evening in 1972, while Tanneberger was still toiling over his test-tubes, he took an unexpected phone call from Gummel, who requested him to come directly to his home. A man of few words, Gummel said, "The people in the Academy believe I need a successor. That will be you." End of conversation. Tanneberger, whose first emotion was complete shock, recalls, "At the time I was 37, and in a very junior position – the last person to head up an international institution with 350 beds and 1,000 staff."

A few months later Gummel died suddenly of a stroke, leaving a power vacuum at the cancer centre. To compensate for his lack of experience, Tanneberger was sent on a year-long programme visiting cancer centres around the world, including Roswell Park Memorial Hospital in Buffalo, New York, the Karolinska Institute in Stockholm, Vienna's Institut Krebsforschung, the All-Union Cancer Centre in Moscow and the Imperial Cancer Research Fund in London. "The opportunity to take time out to learn managerial skills was a great gift to me," he says.

This was not Tanneberger's first experience of overseas travel and the West. His interest in cell biology and tissue culture had given him access to the international science stage, when he became a member of the European Study Group for Human Tumour Cell Investigation. Here he attended overseas meetings with people like Jack Ambrose, Sam Franks, Gio Astaldi, Hans Limburg, George Barski, Marc Mareel and Luciano Morasca. Visiting West Germany he had his fair share of 'John le Carré' experiences, where attractive women knocked on his hotel bedroom door late into the night, declaring their undying love. "It was Cold War," he says with a laugh. "I never felt tempted to defect. The GDR had provided me with ten years of education, and I felt obliged morally to repay what I received. Besides, my family were in East Germany."

In 1970 Tanneberger married Sigrun, a theatre student he met while first working in Berlin. Their children, Thomas (an agriculture publisher and journalist), Katharina (a psychiatrist) and Franziska (an environmental scientist), were born between 1970 and 1978. With Tanneberger working long hours and travelling a lot, childcare was left to his wife. "She did a great job, and I've always had the philosophy that it's important to spend quality time with children. The small amounts of time we had together were highly organised, and on holiday I taught them all to ski or sail," he says.

Cancer control in the GDR

Cancer care was well organised in the GDR, remembers Tanneberger. Tobacco advertising was not permitted and screening systems were in place, with Pap smear programmes introduced in 1976 for cervical cancer, lung X-rays offered to everyone over 40, and a programme to teach breast self-examination to women. The country had a national cancer registry and a national

cancer plan, which included the recommendation that surgeons should only operate if they performed a minimum of 100 similar procedures each year. The net result was that cancer mortality in East Germany was significantly lower than in West Germany. Tanneberger's institute was appointed a WHO Collaborating Center.

Tanneberger felt that the GDR had a great deal it could teach other countries about cancer organisation. In 1978, while director of the Robert Rössle Institute, he joined the UICC (International Union Against Cancer) faculty to teach doctors in India about chemotherapy. In this capacity, Tanneberger had memorable talks with Indira Ghandi, then prime minister, about the cancer situation in her country and entered into a correspondence with her. The visit sparked in him an enduring interest to help cancer patients in the developing world.

On the downside, says Tanneberger, GDR medicine lacked not only instruments and drugs, but also nurses and cleaners, due to the lack of immigration. "Every day we had to think creatively about how to get hold of new drugs, equipment and staff." Eventually he joined the Socialist Unity Party of Germany (SED). "To help my patients I felt that it was really important to get to know influential people. I also had to keep up relations with the STASI – the secret police – because this was the single institution that could help if our western equipment was out of order. For the benefit of my patients I'd have been willing to make a contract with the devil himself," he says, adding that "my partners in the GDR establishment were not devils, but politicians making errors, like myself, including people who had fought many years against Hitler, like my friend Hans Lautenschläger."

Towards the close of the 1980s Tanneberger found himself 'engaged' by the idea of 'perestroika' that was emerging in Russia. At home there were rumblings, with staff meetings called to challenge his authority. "The clarion call was 'Remove your chiefs'. Questions were asked about my foreign travel, the director's privileges (like a personal parking space) and my membership of the SED," he says. "When I could no longer see any chance of continuing to work for my ideas, I took up the President of the Academy of Sciences' offer of extended leave," he says, adding that it was the open hostility of former friends and colleagues that he found most upsetting.

Swords into ploughshares. This former Nazi military prison in Anklam, north Germany, is now home to the Otto Lilienthal Peace Centre, which Tanneberger initiated in 2004 and which occupies much of his time and energy

Tanneberger never returned to the job: after unification less than 10% of university professors from the GDR retained their chairs. "An entire generation of academics was eliminated – it was both a personal tragedy for them and for Germany," he says.

Determined to continue working, and to support

"A generation of academics was eliminated – it was both a personal tragedy for them and for Germany"

He saw first hand the suffering of families, something he says doctors working in hospitals rarely do

his family, Tanneberger was employed between 1990 and 1991 as a consultant to the WHO, undertaking fact-finding trips to India, Bangladesh, Korea and Albania to gather evidence to develop cancer control programmes. "The break was a godsend, giving me both time to reflect on what had happened and the opportunity to do something tangible for developing countries," said Tanneberger.

Supporting dignity at the end of life

Salvation, and the start of a totally new chapter in Tanneberger's life, came in the form of a job offer from the Associazione Nazionale Tumori (ANT), a non-profit organisation based in Bologna, Italy. ANT, launched by Franco Pannuti in 1978, promotes the philosophy of 'eubiosia', guaranteeing terminally ill patients the basic human right of dignity in their own homes until the end of their life. The term 'eubiosia' was chosen, says Tanneberger, "to counteract the triumphant march towards euthanasia" in Europe, which ANT sees as the medical and social inability to achieve a harmonious end to biological life.

Taking up the post of head of quality control in 1993, Tanneberger's job was to oversee the work of the 250 doctors operating the 'hospital at home' initiative in the community.

Practically every day Tanneberger went into four or five patients' homes – he estimates that overall he met an astonishing 20,000 families living with cancer. He saw first hand the suffering of families, something he says doctors working in hospitals rarely have the opportunity to fully appreciate. "We should never consider patients in isolation, and we should never forget that, for the doctor, an operation or any examination is a 'routine' procedure, but for the patient it is often a unique event in his life."

The experience inspired him to write a book,

An internationalist. Tanneberger has always looked for ways to put his experience to use in poorer countries. ▲ Visiting a family in New Delhi, 1992, while working with CanSupport, which provides home-based palliative care ◀ Presenting proposals for a national anti-cancer plan for Bangladesh to leading policy makers, including the ministers for health, education and information, 1991

Peace work. Tanneberger's commitment to a world free from war brought him into contact with Pope John Paul II, in 1982, when he joined a group of scientists in Rome to elaborate the text of the Vatican's Declaration of Prevention of Nuclear War

One of My Family has Cancer: What Can I Do?, which provides practical advice for relatives on things like caring for the dying and how to talk to them. From his time at ANT he feels strongly that adult children taking care of their dying parents should be given the same employment rights to stay at home as parents caring for new-born children. This view was reinforced when he extended the ANT programme to developing countries, and found that cancer patients in places like India were never alone, and received far more support from family members. "In the old times people died with their families gathered round to say goodbye. Now all too often families call the emergency services and they die in the intensive care unit. Families have to learn to let nature take its course," he says.

There are also implications here for euthanasia, he adds. "The real risk of legalising euthanasia is that the state will not feel pressure to develop palliative care." Tanneberger is also troubled by the aggressive use of chemotherapy near the end of people's lives. "We are living now in a time of overuse of anti-neoplastic drugs. I have changed a little bit from a front runner to a warner of cancer chemotherapy," he says smiling.

While professionally rewarding, the move to Italy led to the breakdown of Tanneberger's marriage. He and his wife, who remained in Germany, gradually drifted apart, going their separate ways in 2000. The break, he says, was the ultimate price the family paid for the fall of the Berlin Wall. Prior to that, they had been a 'good family'.

Today Tanneberger is semi-retired, although still working as a consultant to the ANT, and as a part-time professor in palliative oncology at the University of Bologna. His other duty is to fight against cancer in developing countries, working with the European School of Oncology (ESO) and the International Network for Cancer Treatment and Research (INCTR). "I try to meet the two great challenges for oncology in the 21st century: dignity of life by better palliative cancer care in the industrialised world – where cancer is becoming more and more a 'natural cause' of death – and less death from cancer in developing countries, where cancer is exploding."

Hobbies include sport, as always in his life, and writing. Drawing on his experiences in both war time and oncology, he has published two books on the lives of the ordinary people he encountered.

Globalisation for peace and health

Undoubtedly his overriding enthusiasm is for the Otto Lilienthal Zentrum für Friedensarbeit, a peace centre that he initiated in 2004 in Anklam, north Germany. This idea developed over decades out of his meetings with outstanding persons like Pope John Paul II, Linus Pauling, Umberto Veronesi, Nikolai Blochin and Vittorio Prodi.

"The $1,400 billion spent globally on war for oil each year would be far better spent solving fundamental world problems like cancer, climate change, the energy crisis and AIDS. We need this money to control the real threats to the world, rather than the man-made ones," he says.

Oncologists, he maintains, have a vital role to play. As he says at the end of Cancer in Developing Countries, a book he co-edited with Franco Cavalli, "We live in a world of military and financial globalisation but we need a globalisation for peace and health. Oncologists can make significant contributions to overcoming this historical error, and will be motivated by the enormous and unnecessary suffering of millions of cancer patients."

Until close friends tell him he is "too old to talk", Tanneberger vows to continuing fighting his personal battles against war and cancer. On current form he hasn't got anything to fear for a while.

If nothing is done...

Prize-winning article tells the story behind falling cancer mortality rates

The more we know about cancer, the harder it becomes to present a coherent and accurate picture of the nature of the threat and what can – and what cannot – be achieved through changing lifestyles, screening and investing in the search for a cure. **Ulrich Bahnsen** won a Best Cancer Reporter Award for his comprehensive article in the leading German weekly *Die Zeit*, which is republished below.

Cancer is a complicated disease. There are 230 different types of cancer. It occupies tens of thousands of doctors and scientists. It is big business. And if nothing is done it will kill more than 200 million people – one in four of all Europeans and Americans alive today.

Elizabeth Ward records the horrors. Year by year she and her colleagues in the American Cancer Society (ACS) collate the figures which speak of so much hope, anxiety, living, suffering and dying: new cases, cure rates, survival times, mortality.

It is hardly an uplifting activity, but Elizabeth Ward is upbeat. She has encouraging news. Fewer and fewer people are dying of cancer – even though more are developing the disease. American epidemiologists are convinced that they are witnessing the start of a continuing decline. "It is a robust trend," says Ward, "and we expect numbers to fall further in the next few years."

In Europe, too, there is a growing mood of confidence. Nevertheless, cancer is still a long way from being conquered. The decline starts from a high level: 553,888 people in the US died from cancer in 2004, but that is nevertheless 3,000 fewer than in the previous year. In 2003 the researchers had already recorded a lower number of deaths than in 2002. In Germany, deaths from cancer peaked in 1993. Since then the mortality figures have fallen by around 4,000 cases per year.

The evidence on the causes of the long-awaited turnaround now seems clear. On this point the epidemiologists are unequivocal. The breakthrough on the cancer front, says Ward, is primarily the result of prevention and early diagnosis. The celebrated advances in cancer medicine have apparently made only a minor contribution to the success story.

Ulrich Bahnsen

The health researchers' verdict is that it will be possible to reduce cancer deaths significantly, provided that politicians, and in particular the general public, adhere to the policy of prevention, or at least early diagnosis followed by prompt and state-of-the art treatment: this is the new success strategy. According to Otmar Wiestler, director of the DKFZ (German Cancer Research Centre), preventive oncology – long

Comprehensive coverage. This well-researched piece was the first in a series of three – the subsequent article looked at current efforts to improve the care of German cancer patients, followed by a piece exploring the late effects of treatment

regarded as indispensable in the US – has so far been completely neglected in Germany.

70,000 DEATHS COULD HAVE BEEN AVOIDED

Every year Germany has more than 70,000 cancer deaths that could have been easily avoided. Even though there are particular risk factors for many types of cancer, the majority – and in particular the most frequent types – are influenced by the three fatal factors of smoking, obesity and lack of exercise. Hence, at Germany's first National Oncological Prevention Conference, held in mid-June in Essen, the assembled experts did not want to confine themselves to appeals to politicians. Their call was addressed to the person on the street: cancer prevention is the responsibility of everyone, through giving up tobacco and through an active lifestyle. Even non-smokers can dramatically reduce their risk of cancer.

It is not only the Germans' pot bellies that are held to be dangerous. The researchers are also concerned by the wasting muscles of the nation's citizens. The two together – love handles, plus chicken wings where arms ought to be – are regarded as having particular cancer-causing potential. The proliferating fat tissue floods the body with cancer-stimulating hormones and pumps inflammation-causing signal substances into the blood. By contrast, muscles that are hardened by sport drive away these troublemakers: substances that inhibit the cascade of inflammation are released into the bloodstream by the muscle fibres. Thus people who are unfit and overweight slide even further into a state of systemic inflammation – a condition, in the words of DKFZ director Wiestler, in which cancer can flourish.

Smoking exacerbates the hormonal imbalance of overweight couch potatoes even further. The genotoxic effect of the poisons in tobacco smoke encourages the emergence of cancer, and the smoke contains substances which further stimulate the dangerous inflammation process. Exactly how inflammations promote the formation of tumours is not fully understood. It is likely that they encourage the malign degeneration of stem cells in the organs.

The celebrated advances in cancer medicine have made only a minor contribution to the success story

Nothing can be done about fitness and weight loss unless people agree to take action. Smokers, however, are having change forced upon them. Since 2004 the EU has been taking the battle against nicotine addiction seriously. Even in Germany, smoking bans are due to be imposed. The justification for clamping down on the civil liberties of smokers is the risk inherent in passive smoking, which claims up to 80,000 victims a year in the EU.

It would, however, be naïve to suppose that this move is primarily for the protection of non-smokers. The real aim of the ban on smoking in public places is to protect future generations by thoroughly repressive means. "Smoking bans establish non-smoking as the social norm," says Elizabeth Ward bluntly. In her view social proscription is necessary if the great goal of the health strategists is to be achieved: "All tobacco-dependent cancers are entirely preventable." Lung cancer is not the only form of cancer involved: cancers of the bladder, colon, breast, mouth, oesophagus, larynx and even the pancreas are also stimulated by the toxins in tobacco. One smoker in ten goes down with lung cancer; 90% of cases of the disease occur in addicted smokers.

But one of the worst killers could soon be history. The story also demonstrates the effectiveness of even unintentional cancer prevention. It seems that stomach cancer, which in the middle of the last century was still one of the commonest fatal cancers, has been held at bay by the refrigerator. Since we have taken to keeping food fresh by chilling it instead of by pickling, salting or smoking it, cases of stomach cancer and deaths from it have fallen rapidly. Now that the once rampant stomach ulcer has been conquered too, stomach cancer is likely to become a rarity. Stomach ulcers represent a chronic inflammation of the stomach lining as a result of infection with the stomach bacterium *Helicobacter pylori*; like the toxic substances in conventionally preserved food, it stimulates the emergence of cancer. Deaths from stomach cancer in industrialised countries have fallen by 80% since 1950.

This "unplanned triumph", in the words of the US doctor Christopher Howson, is now likely to be followed by a strategic victory. Doctors are hoping that cervical cancer will soon be eradicated by means of a vaccination. Worldwide some 250,000 women per year die of this cancer. The disease is always the long-term consequence of an infection with a papilloma virus. In Germany, the death rate has already fallen sharply as a result of smear tests (Pap smears), which enable the cancer to be identified at an early stage. It is hoped that two new vaccines against the papilloma viruses 16 and 18 will finally put the brake on the disease.

However, they have no effect on an already existing infection. Following a resolution of Germany's Standing Vaccination Commission (Stiko), the emphasis will therefore be on immunising girls and young women between the ages of 12 and 17.

Infections lie behind one in five cancers

Experts estimate that one cancer case in five is ultimately caused by a normally avoidable infection. Thus it seems that deaths from liver cancer are also largely preventable. Alongside alcohol abuse, which paves the way first for cirrhosis of the liver and then for cancer, infection with one of the various forms of the hepatitis virus poses the greatest risk. Although the liver infection leads on to cancer in only a small proportion of chronic cases (and then only after many years), the viruses are nevertheless the principal cause of this cancer.

According to the gastroenterologist Markus Cornberg of the medical university in Hanover, testing has revealed that half the liver cancer patients in his clinic are carriers of the virus. At least one million people in Germany are permanently infected with either the hepatitis B (HVB) or hepatitis C (HVC) virus. Since 1992 blood products, previously the principal source of infection, have been tested to guarantee their safety. Yet many people continue to become infected with hepatitis C – drug addicts through exchanging needles, and others through

The real aim of the ban on smoking in public places is to protect future generations

simple foolishness that can put them at risk. "Getting yourself tattooed on the beach during your holiday in Egypt is not at all a good idea," says Cornberg, "One person in five there carries the virus."

Cancer caused by hepatitis B can be even more easily avoided. A vaccine against the virus, which can also be transmitted sexually, has long been available. What can be achieved by a campaign of vaccination against liver cancer was demonstrated 20 years ago by the island state of Taiwan. The government launched a mass HVB vaccination campaign for children in an attempt to control the rampant virus. The incidence of the cancer subsequently fell by half among those who had been vaccinated.

The health strategists would like to be able to report similar successes in other key areas of oncology. They don't want to carry on waiting for the hoped-for breakthrough in the treatment of advanced cancers. According to Michael Bamberg, president of the German Cancer Society, treatments in the late stages of cancer will in future need to be very carefully weighed up. In his view we should instead be spending the majority of the available funds on prevention and screening. "In the case of metastasised tumours we have already missed the bus; we must take pre-emptive action."

A message for you. With its talk of 'the German potbelly' and discussion of the national disquiet over 'repressive' anti-smoking laws, the Die Zeit article addresses key cancer issues in a way readers can readily relate to

This change in thinking is the result of depressing experiences. The bitter realisation is that cancer cannot be conquered by the classical methods of oncology alone. In the 1970s, after spectacular successes brought about by the introduction of chemotherapy, it looked at first as though the war was already as good as won. The experts prophesied that victory over cancer was only a question of time and money. The aim was to halve the number of deaths from the disease by the year 2000. And there were indeed indisputable triumphs: in virtually hopeless cases such as testicular cancer cure rates rose to 90%; for leukaemia they rose to 75%. Likewise, Hodgkin's lymphoma, a type of cancer of the lymph glands, is now regarded as 80%–90% curable.

But since those days, cancer therapy has to a large extent stagnated. In the last four decades industrialised countries and pharmaceutical companies have pumped hundreds of billions of euros into basic research and the development of more effective treatments and new drugs. The American

National Cancer Institute alone has an annual budget of $4.5 billion. And it would be wrong to claim that the money has been pointlessly squandered. Highly effective drugs, ultra-precise radiation techniques and the increased refinements of surgery have increased cure rates for many types of cancer and extended the life expectancy of many patients. They have also improved sufferers' quality of life and reduced the side-effects of treatment which, with justification, were formerly feared. But progress is excruciatingly slow.

At this year's prestigious gathering of experts, the meeting of the American Society of Clinical Oncology in Chicago, it was again made clear that any hope for a 'magic cancer bullet' will remain an illusion. The 32,000 attendees were presented not with therapeutic miracles but with a wide range of small improvements – a couple of new drugs, better chemotherapies, the application to another type of cancer of a drug that has proved itself in a different area. "More of the same", sighed a US reporter resignedly during one of the daily press conferences.

The current situation can be summed up by saying that more and more patients are living longer and better lives with their cancer, but in the end almost as many are dying as 20 years ago. For cancers of the lung and kidney, which tend not to be diagnosed until a late stage, the outcomes of treatment are depressing; for pancreatic cancer they are disastrous.

In the middle of the 1990s, a quarter of a century after US President Nixon had declared the country's 'war on cancer', it was already evident that far-reaching success as a result of new treatments was not going to be as readily achievable as had been hoped. As the experts resigned themselves to the situation, heretics began to raise their voices. In 1997 the epidemiologists John Bailar and Heather Gornik of the University of Chicago caused a stir with a hard-hitting progress report. "The effect of new treatments for cancer on mortality has been largely disappointing," was the researchers' verdict in the *New England Journal of Medicine*; any hope of a substantial reduction in death figures before the year 2000 was "clearly misplaced". The professional world reacted with outrage, but it was impossible to refute the gloomy calculations coming from Chicago.

Early detection has a lot more to offer

As it turns out, Bailar and Gornik were wrong and yet at the same time they were right. When they spoke out, the fall in mortality rates had in fact already begun; it was to continue until the present day – a consequence of the declining number of smokers and the first early detection campaigns. "Cancer is a disease that is easier to prevent than to treat," wrote the oncologist Michael Sporn in *The Lancet*. "Our obsession with curing advanced cancers rather than preventing the disease in the first place or stopping it at an early stage has shifted victory into the far future." A fundamental reorientation was what Bailar and Gornik had also called for. They realised that, alongside intensive research, prevention and screening were key issues that must be accorded the status of a 'national priority'.

The US set up early detection programmes long before Germany. Their success is now apparent. A DKFZ study published in the spring showed that the better prognosis for American breast cancer patients compared with those in Germany is a consequence of the more thorough mammography screening that is carried out in the US. In the US 80% of women aged over 40 are screened in this way. As a result, breast cancer is detected earlier there. Germany did not start to develop a quality-assured mammography programme until 2004.

Early detection does indeed appear to have great potential. According to the German Cancer Society's president, Michael Bamberg, one-third of the common malignant cancers are not detected until metastases are already rife in the patient's body, and more often than not it is they that are the

The bitter realisation is that cancer cannot be conquered by the classical methods of oncology alone

In practice, however, early detection verges on being both a blessing and a curse

killers. "Even with the most modern targeted therapies it is very difficult to achieve a cure in that situation," says DKFZ director Wiestler. In other words: more screening saves lives.

In practice, however, early detection verges on being both a blessing and a curse. Early detection tests are available for only a few types of cancer. Furthermore, most procedures are imprecise. All too often tests give the all-clear when in reality a tumour is already growing; too frequently they report a cancer which is not in fact there or which does not require treatment. As a result patients are lulled into a false sense of security and may skip the next examination because "nothing showed up last time." Many prostate cancer patients, on the other hand, suffer from the consequences of unnecessary surgery – because the check-up does not reveal whether what was found was a rare type of aggressive prostate cancer or one of the forms that will never prove fatal.

Although there is an absence of clear evidence, colonoscopy is regarded as an effective method of early detection. The examination can be used not only to identify early signs of cancer; suspicious colon polyps, the precursors of colon cancer, can be immediately removed, thus preventing the cancer developing. Despite this, the procedure is not as popular as it deserves to be. Scarcely 10% of Germans undergo screening. "A lot can be done for colon cancer," says DKFZ epidemiologist Nikolaus Becker, "and quite a lot with quality-assured mammography."

Genome research may predict individual risk in the future

In the eyes of the experts, a crucial means of further reducing deaths from cancer will be the development of more precise early detection techniques. Here the results of basic research are giving grounds for hope. In tumour biology the age of the genome has dawned. While scientists previously had to search painstakingly for individual genetic defects within tumours, researchers of the Cancer Genome Atlas Consortium are now decoding the complete genetic make-up of tumours. The aim is to systematically identify all the genetic changes that take place in cancer cells. The $100m pilot project for the Cancer Genome Atlas is already under way. As a first step researchers are decoding and analysing the genetic make-up of the cancer cells of 500 patients with ovarian cancer, lung cancer and the almost invariably fatal brain tumour glioblastoma multiforme. It is already clear that defects in hundreds of genes control the emergence, growth and metastasising of cancer sites. Gene profiling opens up new opportunities for drug treatments, but its primary purpose is to facilitate effective diagnostic procedures.

The American drugs authority has already licensed the first genetic cancer profiler. The test systems, which go under the names of MammaPrint and Oncotype DX, measure the activity of a number of genes in breast cancer samples. The results can be used to predict whether a patient requires chemotherapy after surgery in order to prevent the tumour returning.

This is but the first move in a new era of cancer medicine. Similar procedures for other types of cancer are already at an advanced stage of development. For example, scientists at the University of Cologne are working on a test that would actually predict lung cancer. Doctors could then intervene before the patient becomes ill. However, it will be some years before the wonder tool is ready for clinical use. It takes almost as long to validate such diagnostic tools as it does cancer drugs.

Until then, we must continue to make full use of all available means of cancer prevention. Everyone can do something. Elizabeth Ward suggests as a starting point "Smoking? Don't even think about it."

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Bringing truths about cancer to new audiences

The UICC's Reel Lives film festival showcases 33 of the best

➜ Peter McIntyre

When it comes to challenging taboos and giving a voice to ordinary people with extraordinary stories, film can be immensely powerful, as was shown at the first ever Reel Lives: Cancer Chronicles Film Festival, held in Geneva at the end of August.

"I have to say I approached the festival a little cynically," admitted Linda Garman, one of the winners. "I mean who wants to go and see a film festival about cancer?" She soon changed her mind. "I had an amazing week. I saw that the goal was to make this a life-affirming experience and it certainly worked for me. There were some great films that were obliquely about cancer, but all of them about life."

Reel Lives, the first ever film festival about cancer, attracted more than 250 entries, of which 33 films from 16 countries were shown in the final competition in Geneva in August, in parallel with the World Cancer Congress. Viewings were well attended and the festival already looks to have established itself.

Silvia Perel Levin, festival producer for the International Union Against Cancer (UICC), said, "Part of the UICC mission is to raise awareness of cancer and to break the stigma. This UICC film festival provides a critical voice in doing so, using one of the most popular art forms. We wanted to reach out to the general public."

The variety was extraordinary – from 30-second public service announcements to 90-minute documentaries – and the quality high. *Freeheld*, winner of the Best Short Documentary Oscar in Hollywood, was shown here but did not win. There was a lot of honesty too. These films are full of fight and commitment, but do not all end in victory.

The overall winner, *Chrigu*, is a home-grown story as much about friendship as about cancer. When young Swiss filmmaker Christian Ziorjen (Chrigu) was diagnosed in 2005 with PNET, a form of Ewing's sarcoma, he made a film about his feelings and his treatment. He ended his film by saying that if he ever had to go through treatment again, he would probably kill himself. But when the cancer returned a few months later, he felt very differently and he turned to his filmmaker friend Jan Gassmann for help. "Let's make a movie together – I'll just drop out at some point," he told him.

Jan knew little about cancer but a lot about friendship. "The only way I could relate to this topic and understand was that he was my friend and he could explain it so well and tell me his thoughts. The most important thing is to have trust between the two people. We were making a film together like we always did."

Much of the film was shot around the Inselspital University Hospital in Berne, where Christian was treated until his death in November 2005 at the age of 22, but scenes are intercut from another journey the two had made together three years earlier, making this a film as much about life as about dying.

"Christian said he wants the film to be funny so that people can laugh. That

▲ Breaking taboos. Christian Ziorjen (Chrigu), a budding young film maker, co-directed the winning film *Chrigu* in the final months before his death aged 22

▶ Busting myths. Linda Garman won this Best Reportage award for her film *The Truth About Cancer*, which follows patients with metastatic disease, who know that the odds are stacked against them

is something I was really trying to achieve, because those four months I spent with him at the hospital were not depressing and we had a lot of fun. There were hard times, but I didn't want to give the viewer the feeling that it was all sad."

The film had a cinema release in Switzerland, where it was seen by 20,000 people. The award would have meant a lot to Christian says Jan Gassmann. "He told me he wanted to achieve something to work against this taboo of death. He wanted the film to be seen and it gave me a good feeling that people talked about it, not only the people usually interested in cancer, but a lot of young people as well."

The Best Reportage film, *The Truth about Cancer*, begins in a similar place to *Chrigu* but makes a very different journey. Linda Garman started to make a film with her husband Larry when he was diagnosed with mesothelioma in January 2000, confident it would be an upbeat story. When, after waves of treatment, he died, what Linda calls her 'naïve faith in medical progress' was swept away.

"As the daughter of a space programme engineer, I had grown up with an unquestioning faith in America's ability to solve problems with science and technology. So nothing, nothing at all, prepared me for what happened 30 years later when my husband died of cancer."

Six years later she went back to the Boston hospitals where her husband had been treated, to ask some probing questions about the nine out of ten

"He told me he wanted to achieve something to work against this taboo of death"

Real lives. Vinay Charkravarthy, a trainee doctor, featured alongside his wife Rashmi in the film *The Truth About Cancer*. The film leaves the couple optimistic as Vinay has a bone marrow transplant, but after the film was finished, the cancer returned, and Vinay died earlier this year

OTHER WINNING FILMS

Best Personal Story

The Art of Living, by Sutapa Biswas, India.

Painter Sambhu Das was diagnosed with cancer of the larynx in 1998, but never lost focus on becoming a successful artist

Best Film from an Organisation

Les enfants de l'Avenir, by Bruno Peyronnet, Morocco.

A child with cancer is cared for at Rabat Children's Hospital and at La Maison de L'Avenir

Best Public Service Advertisement

The Hookah, by Broadcast, Israel.

Smoke from the hookah (narghile) forms the words *banana*, *apple*, *cherry* and *strawberry*, as the voice-over asks, "In which flavour do you prefer your cancer?"

Honourable mentions

The Breast Cancer Diaries, by Linda Pattillo, USA.

Emily's Story, by Bruce Postman, USA.

La guerre contre cancer, by Sylvie Gilman and Thierry de Lestrade, France.

How Long is a Piece of String? By David Hayes, Australia.

Any Questions, by Mark Dube, Canada.

people with metastatic cancer who do not survive more than five years.

Her 90-minute film is relentlessly honest. It records successes – Glivec and childhood cancers – but mostly it challenges what Garman calls 'the Lance Armstrong myth', that if you fight hard enough and throw enough resources at a problem you will conquer it.

Among the patients featured is Jamie Klayman, who has metastatic pancreatic cancer and faces her disease with a tough candour, entering phase I clinical trials understanding that she is clinging to straws. "It does not seem to be the right thing to just sit and wait and do nothing." She feels a pressure to survive and not 'fail'. Her father insists that it is just a question of finding a doctor with a more positive attitude.

Shortly before her death in November 2007, Jamie says, "I thought about the term 'survivor' and there should be some term for people who struggle and don't make it through. I would hate for people to think that those people who didn't survive didn't want to, or didn't have the will to survive."

This thoughtful and well-researched documentary film has already been seen by 3.5 million viewers on PBS in the US, and can be viewed online at www.pbs.org/wgbh/takeonestep/cancer/index.html

Linda Garman says her main aim was to challenge media myths. "We have a cancer industrial complex here in the United States and the media feed into it, helping the cancer field to hype things that shouldn't be hyped. You have really irresponsible coverage of so called breakthroughs. I am old enough to have lived through several of them, interleukin, interferon, Glivec. It is not that those drugs did not prove to have utility for a small window of cancers; it is just that the way that we cover that in the media is so over the top, and the coverage does not ask the right questions.

"At the other end of the spectrum is the media as personified by the Oprah Winfreys of the world. They invite cancer patients onto their show who say the reason they are alive is because they practice yoga and churn up green drinks in the blender every morning, when in fact those people have treatable forms of cancer with the best that medicine can offer right now.

"At either end of the spectrum, you are doing a huge disservice to the cancer field, to patients and to the decision we make as a society about resources and what we should focus on."

The Truth about Cancer is also a story of love, family life and patient–doctor relationships. Linda says, "When they awarded and recognised my film when there were so many other good ones in the festival, I was really overcome. It honours my husband's memory and his family. It was a magic moment."

"I would hate people to think that those who didn't survive didn't want to, or didn't have the will"

Concomitant difluoromethylornithine/sulindac chemoprevention of colorectal adenomas: a major clinical advance

Michael Sporn and Waun Ki Hong

Combining two drugs, i.e. difluoromethylornithine and sulindac, at low doses has been shown, for the first time, to provide both great efficacy and great safety for clinical colon cancer prevention.

Summary

In a randomised, placebo-controlled, double-blind clinical trial by **Meyskens et al**., the combination of difluoromethylornithine and sulindac has been shown to be strikingly effective for prevention of sporadic colorectal adenomas (**Difluoromethylornithine plus sulindac for the prevention of sporadic colorectal adenomas: a randomized placebo-controlled, double-blind trial** *Cancer Prev Res* 1:32–38). This concomitant use of two drugs to suppress the progression of preneoplastic lesions represents the first major clinical success of the application of the principle of 'combination chemoprevention'. Neither drug alone has previously had clinical utility at the low doses used in this trial. The combination of the two agents has provided synergistic efficacy in suppression of carcinogenesis, while minimising any undesirable adverse effects. This study should be the impetus for further clinical investigation of the use of multiple drugs for chemoprevention of cancer.

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As we have noted elsewhere,[1] the recent report[2] of the combined use of difluoromethylornithine (DFMO) and sulindac to prevent recurrence of colorectal adenomas in patients at high risk of such malignancies is a spectacular advance in the field of cancer treatment. The study by Meyskens and colleagues represents the first clinical validation of the concept of using more than one drug for effective chemoprevention, a theory that was first proposed many years ago.[3,4]

Chemoprevention is still a very controversial approach to the overall control of malignancy, particularly because of concerns about undesirable adverse effects of chemopreventive agents when given to asymptomatic patients over prolonged periods of time. In their clinical study, Meyskens and coauthors have clearly shown that unwanted adverse effects can be prevented by using the lowest possible doses of two drugs in a combination regimen, a strategy that can facilitate synergistic action between two agents while minimising their individual potential for toxicity. By contrast, conventional chemotherapy for treating advanced malignancy traditionally entails escalating the dosage of any therapeutic agent to its maximum tolerated level, and thus adverse effects are frequent. In the DFMO and sulindac chemoprevention study, the investigators used a brilliant, counterintuitive

'dose de-escalation' strategy. They first determined the lowest possible dose of either DFMO or sulindac that might provide a useful biological response, and then used these doses of the two drugs in combination. In previous clinical trials, neither DFMO nor sulindac has been particularly active or free of adverse effects as single agents.

The results obtained in the Meyskens et al. study are stunning. In this trial involving almost 300 patients, the drug combination reduced the overall incidence of adenoma recurrence by 70%, from 41% in the control population to 12% in the patients treated with the drug combination. Most striking were the effects of DFMO and sulindac on the number and severity of new adenomas. In this 36-month trial, only one patient in the treated group had multiple adenomas when examined at the final colonoscopy compared with 17 patients in the placebo control group. The severity of any adenomas that did recur was also markedly reduced by the DFMO and sulindac combination: 11 patients in the placebo group had adenomas classified as 'advanced', whereas such a lesion was found in only one patient in the combination therapy group. These preventive effects of the combination regimen were highly significant ($P<0.001$); such results have never been obtained in any previous clinical chemoprevention study.

An important point to note is that it is now clinically possible to minimise adverse effects of chemopreventive drugs by employing study designs that utilise dose de-escalation strategies, together with the combined use of multiple agents that will act synergistically. This approach was the aim of the original hypothesis of 'combination chemoprevention'. It is clear that dose escalation strategies that might be useful for clinical chemotherapy of advanced malignancy are not viable approaches to clinical chemoprevention of early, preneoplastic disease. In this regard, the unfortunate toxic events that have resulted from long-term administration of high doses of celecoxib[5] or rofecoxib[6] represent paradigms one wants to avoid in the future development of the entire field of chemoprevention of cancer.

So what is the ultimate significance of this new clinical advance in chemoprevention of preneoplastic lesions in the colon? The concept that the capacity to control the progression of preneoplastic lesions represents an ideal approach to treating cancer is hardly a new one. Indeed, at a conference on Early Lesions and the Development of Epithelial Cancer, held at the National Institutes of Health in Bethesda, MD, more than 30 years ago, this strategy was clearly enunciated. A final summary statement from the three-day international conference published in *Cancer Research* is as topical and relevant today as it was in 1975 when it was written.[7] It reads as follows:

> "The development of cancer in all of these organ sites is a prolonged process, which may take 20 years or more in humans to reach its invasive stages. Before invasive malignant disease occurs, various preneoplastic changes occur in all of the above organ sites. Although these preneoplastic changes have not been generally considered to be 'cancerous' (i.e. in the classical, clinical diagnostic sense of the term), they are definitely an integral part of the process of development of cancer. Because the prognosis for invasive malignant disease becomes worse as the stage of the disease increases, it is essential that more-intensive efforts be devoted to study of the disease process in its preneoplastic states.
>
> "Greater effort must be devoted to development of new methods for detecting individuals at increased risk and to development of more accurate diagnostic markers, both of which will make possible a more meaningful definition of the various stages of preneoplasia and their relationship to invasive neoplasia. It is not yet clearly known at which stages the preneoplastic process is reversible and when it becomes irreversible. It is essential that a clearer definition of these stages be obtained. Greater effort also must be devoted to development of new methods of prevention of invasive cancer by application of treatment during those preneoplastic stages that have a very high likelihood of progressing toward invasive cancer. Further research on pharmacological, immunological, and surgical approaches to prevention and control of invasive disease while it is still in the preneoplastic state is thus critically needed."[7]

Unfortunately, more than 30 years later, the entire field of preneoplasia research still suffers from neglect, as more and more effort is devoted to seeking ultimate cures of advanced disease. Meyskens and colleagues' new clinical study on combination chemoprevention of colorectal adenomas with DFMO and sulindac represents a new advance that hopefully will help to redress the balance between cancer prevention and therapy and to redirect more effort toward control of early lesions. Such effort is critically needed.

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

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The ROC 'n' role of the multiplex assay for early detection of ovarian cancer

Alpa Nick and Anil Sood

The sensitivity and specificity of CA125 for early detection of ovarian cancer is improved when analysed in combination with novel biomarkers, although further validation studies are required to confirm the clinical utility of the multiplex assay.

Summary

In order to overcome the significant mortality associated with ovarian cancer, a highly sensitive and specific screening test is urgently needed. CA125 is used to assess response to chemotherapy, detect recurrence and distinguish malignant from benign disease; however, this marker is elevated in only 50%–60% of stage I ovarian cancers, making it inadequate for early detection of malignancy. Here, we discuss **Visintin et al.'s** attempt to validate a novel multiplex assay that uses a panel of six serum biomarkers – leptin, prolactin, osteopontin, insulin-like growth factor II, macrophage inhibitory factor and CA125 (**Diagnostic markers for early detection of ovarian cancer** *Clin Cancer Res* 14:1065–1072). The study, included 362 healthy controls and 156 patients with newly diagnosed ovarian cancer. The final model yielded 95.3% sensitivity, 99.4% specificity, a positive predictive value of 99.3% and a negative predictive value of 99.2%. These results indicate potential utility of this assay for early detection of ovarian cancer, although further validation is needed in a sample set representative of the general population.

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Ovarian cancer is the deadliest gynaecologic malignancy in the US, with an estimated 15,520 deaths in 2008. This high mortality reflects the poorly understood preclinical state of ovarian cancer and the fact that its nonspecific symptoms are typically unrecognised in the earliest stages of disease. Almost 70% of patients present with advanced-stage disease; however, the five-year survival for women with either stage I or II ovarian cancer is good (92% for localised disease versus 30% for advanced disease), as is the survival for those with small-volume advanced-stage disease following optimal cytoreduction.[1] The search for biomarkers that detect ovarian cancer before an increase in tumour burden is justified by these facts.

In order to be adopted as a screening strategy, most researchers agree that a biomarker must achieve a minimum positive predictive value (PPV) of 10% along with a minimum specificity of 99.6%.[2] Historically, CA125 has proven useful in ovarian cancer for assessing response to chemotherapy, detecting disease recurrence and distinguishing malignant from benign masses. More recently, serum and tissue expression of CA125 has been linked to prognosis, particularly in late-stage ovarian cancer.[3] Nonetheless, elevated CA125 levels are noted in only 50%–60% of patients with stage I disease.[4] New modalities are therefore needed in order to improve the likelihood of early detection of ovarian cancer. Jacobs and colleagues examined the merit of a multimodal

approach to screening for ovarian cancer by incorporating bimanual examination and ultrasonography with CA125 testing; however, this combined approach yielded a PPV of only 21%.[5] In addition, the majority of women with screen-detected ovarian cancer were diagnosed with advanced disease, highlighting the need for early detection.[5] Other researchers have evaluated the benefit of combining CA125 with novel biomarkers in an effort to improve the sensitivity and specificity of CA125 measurement alone. One such example is the combination of CA125 and human epididymis protein 4, resulting in 76.4% sensitivity and 95% specificity, which was better than either biomarker alone.[6] Nevertheless, there remains room for improvement.

In a recent study, Visintin et al. validated a panel of six serum biomarkers (leptin, prolactin, osteopontin, insulin-like growth factor II, macrophage inhibitory factor and CA125) that showed differential expression in disease-free individuals and patients with ovarian cancer on microarray analysis.[7] This study serves as a follow-up to a similar study in which a panel of four novel biomarkers (leptin, prolactin, osteopontin and insulin-like growth factor II) exhibited 95% sensitivity, 95% specificity, 95% PPV and 94% negative predictive value for detection of ovarian cancer.[8] Although the accuracy of this combination of four biomarkers is a considerable improvement on current screening methods given the low prevalence of ovarian carcinoma, there is still need for a test with greater specificity. Consequently, these investigators added CA125 and macrophage inhibitory factor to their four-plex assay in an attempt to further improve specificity. The authors evaluated the serum concentration of the six markers in a training set (181 controls and 113 patients with newly diagnosed ovarian cancer) and validation set (181 controls and 43 patients with newly diagnosed ovarian cancer).[7] The area under the receiver operating characteristic (ROC) curve was used to calculate the sensitivity at 95% specificity for each marker, and four models were used to combine markers in the training and test sets. This analysis yielded a final model that combined observations from both sets to result in a sensitivity of 95.3%, specificity of 99.4%, PPV of 99.3% and negative predictive value of 99.2%.[7]

The authors should be commended for the various strengths of this study, which include the design of a diagnostic panel that permits simultaneous measure of multiple markers by the use of a relatively small volume of patient serum. The evaluation of only six biomarkers is a feasible alternative to a single measurement of CA125, and the inclusion of both patients with early-stage disease and those with advanced cancer shows the utility of the assay for early detection. There are, however, a few limitations. Both study sets represent populations that are enriched for ovarian cancer, with the prevalence of ovarian cancer being slightly higher in the training set than in the validation set (21% versus 19%, respectively). The sensitivity and specificity of the assay decreased in the validation set compared with the training set. Although the combined assay remains a better test than detection of CA125 alone, one must be aware that there could be further decline in the specificity of the assay as sample size increases, given that the prevalence of ovarian cancer in the validation set was considerably higher than in the general population. The authors attempted to validate the assay with a unique validation population. Nevertheless, the final model involved combination of the test and training sets, making it imperative that there should be further validation before use of this assay in a clinical setting. Also, although this assay distinguishes between patients with epithelial ovarian cancer and healthy controls, it may not be specific to ovarian cancer, thereby potentially decreasing its utility in a clinical setting. Furthermore, CA125 levels are known to be elevated in certain benign gynaecologic diseases, which may further affect the accuracy of this screening modality. The authors matched cases to controls only on the basis of stage and histologic grade, so other baseline differences might have affected the assay results. Finally, several questions arise concerning sample handling and processing that could ultimately affect specimen quality and assay reproducibility and reliability.

In conclusion, this study provides a potential viable alternative to screening for CA125 alone for the diagnosis of ovarian cancer. Nevertheless, further prospective multi-institutional evaluation will be required to validate this six-plex assay as a feasible tool for diagnosis and screening of ovarian cancer in the general population.

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

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NEWSROUND

Selected reports edited by Janet Fricker

Intervention by nurses can help combat depression in cancer patients

→ The Lancet

A team of Scottish researchers has shown that cancer patients offered a depression care intervention, delivered by specially trained oncology nurses with no previous psychiatric experience, showed improvements in symptoms of depression compared to patients offered usual care. The beneficial effects of the "depression care for people with cancer" package (DCPC) were found to be sustained at 12 months' follow-up, to the surprise of the investigators.

Michael Sharpe and colleagues, from the University of Edinburgh Cancer Research Centre, Western General Hospital, Edinburgh, Scotland, undertook the SMaRT (Symptoms Management Research Trials) oncology 1 trial to study the use of the DCPC package, which had been originally designed for the treatment of depression in primary care.

In the study, funded by Cancer Research UK, 200 patients – all with a cancer prognosis of more than six months (to ensure they could complete the trial) and major depression – were randomised to receive the usual care of antidepressants and mental health referrals or usual care in addition to the DCPC programme. Patients allocated to the DCPC arm were offered an average of seven one-to-one consultations over three months with a specially trained cancer nurse. The sessions aimed to help patients to understand depression and its treatments, including antidepressants, and provided problem-solving strategies to help patients overcome feelings of helplessness. The nurses also communicated with each patient's oncologist and primary care doctor about the management of their depression.

Following the initial treatment, the nurse monitored the patient's progress by telephone and provided optional booster sessions if needed. Depression levels were measured using the self-reported Symptom Checklist-20 depression scale (range 0–4), and also by interview at three, six, and 12 months for both groups.

The nurses, who had no previous experience of psychiatry, were trained to deliver the intervention using written materials, tutorials and supervised practice over a period of at least three months.

Sharpe and colleagues found that patients who received DCPC had a lower depression level – by 0.34 on the five-point scale – than those who did not receive DCPC. The treatment group also had a major depression rate that was 23% lower than in the usual care group. After 12 months, the benefits from the DCPC intervention were still evident. The DCPC intervention also improved anxiety and fatigue, but did not improve pain or physical functioning.

In future studies, the team hopes to investigate whether the programme is cost-effective if implemented on a larger scale, and whether the intervention might also benefit patients who have cancers with a poor prognosis, such as lung cancer.

In an accompanying comment, Gary Rodin (Princess Margaret Hospital, University Health Network, Toronto, Canada), wrote: "In a well-designed study, Sharpe and colleagues have shown that trained nurses with no previous psychiatric experience can deliver a cost effective collaborative psychosocial intervention for cancer patients with major depressive disorder. Such multi-component interventions are potentially feasible in cancer treatment centres and can be perceived by patients as less stigmatising than referral to a mental health specialist."

■ V Strong, R Waters, C Hibberd et al. Management of depression for people with cancer (SmaRT oncology 1): a randomised trial. *Lancet* 5 July 2008, 372:40–48

Treatment of depression in patients with cancer. Comment. G Rodin *ibid* pp 8–10

Multiple myeloma: bortezomib increases time to progression

→ N Engl J Med

Adding bortezomib to combination therapy with melphalan and prednisone in newly diagnosed multiple myeloma patients who are

not eligible for high-dose chemotherapy, increased time to progression, a phase III study has found.

For over 40 years the standard of care for newly diagnosed multiple myeloma patients who are not candidates for high-dose chemotherapy has been combination treatment with melphalan and prednisone. More recently, high-dose therapy with haematopoietic stem-cell transplantation has become the preferred treatment for patients less than 65 years, but older patients generally do not tolerate such an approach, which rules this option out for most patients since the median age at diagnosis is approximately 70 years. Jesus San Miguel and colleagues from Hospital Universitario de Salamanca, in Spain, therefore set out to investigate the benefits of adding the protease inhibitor bortezomib to the melphalan and prednisone.

The investigators randomly assigned 682 patients (ineligible for high-dose therapy) to receive nine six-week cycles of melphalan (9 mg/m^2 body-surface area) and prednisone (60 mg/m^2) on days 1 to 4, either alone (for the control group) or with bortezomib (1.3 mg/m^2) on days 1, 4, 8, 11, 22, 25, 29 and 32 during cycles 1 to 4, and on days 1,8, 22, and 29 during cycles 5 to 9. Results show time to disease progression among patients receiving bortezomib in addition to melphalan-prednisone was 24.0 months, compared to 16.6 months for the control group (HR 0.48; P<0.001). There were also significant improvements associated with bortezomib therapy for the rate of complete response, time to subsequent myeloma therapy and overall survival.

Grade 3 adverse events were more frequent in the bortezomib group (53% vs 44%, P=0.02), but no significant differences in grade 4 events were found.

Superior efficacy in the treatment of myeloma, say the authors, has now been shown with both bortezomib and thalidomide. "Melphalan and prednisone alone can no longer be considered the standard of care in patients who are 65 years of age or older," they conclude.

■ Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. JF San Miguel, R Schlag, NK Khuageva et al. *N Engl J Med* 28 August 2008, 359:906–917

Pegylated interferon delays recurrence of melanoma

➜ The Lancet

Administration of pegylated interferon alfa-2b significantly improves recurrence-free survival in patients with resected stage III (lymph-node metastatic) cutaneous melanoma in comparison to observation alone, according to a study by the EORTC. No difference, however, was found in overall survival.

Although adjuvant therapy with interferon alfa is widely used for melanoma patients with stage IIb and stage III melanoma, who are at high risk of recurrence after definitive surgery, controversy remains over whether it is effective enough to justify routine use, given the toxicity of the treatment.

The phase III study (EORTC 18991) principal investigator, Alexander Eggermont (Erasmus University Medical Centre, Rotterdam, Netherlands), set out to investigate whether using pegylated interferon could facilitate prolonged exposure while maintaining tolerability.

Patients with resected stage III melanoma were randomly assigned to receive pegylated interferon alfa-2b (n=627) or observation (n=629). Patients were started on induction doses of 6 µg/kg per week for eight weeks, then moved on to maintenance doses of 3 µg/kg per week for an intended duration of five years. Participants were assessed for recurrence and distant metastases every three months during the first three years, then every six months. After a median 3.8 years of follow-up, 328 recurrence events occurred in the pegylated interferon group compared with 368 in the observation group (HR 0.82, 95% CI 0.71-0.96; P=0.01). Distant-metastasis-free survival was longer in the interferon group than in the observation group, although this difference was not statistically significant. There was no difference in overall survival between the two groups.

The benefits were greater for patients with a less heavy disease burden. Among patients with microscopic nodal disease, there were fewer recurrences or deaths in the interferon group than in the observation group (P=0.016); but among patients with palpable nodal disease, similar numbers of recurrences (P=0.119), distant metastases (P=0.53) and overall survival (P=0.91) were seen in the two groups.

In patients with microscopic disease who had an ulceration in the primary tumour (n=186), pegylated interferon seemed to reduce the risk of recurrence, distant metastasis and death, regardless of how many nodes were involved.

Grade 3 adverse events occurred in 246 patients (40%) in the interferon group and 60 (10%) in the observation group, while grade 4 adverse events occurred in 32 patients (5%) in the interferon group and 14 (2%) in the observation group. The most commonly observed side-effects were fatigue and depression.

"Our data suggest that pegylated interferon alfa-2b could be an option for adjuvant treatment of patients with resected high-risk melanoma, especially those with lower nodal tumour burden," write the authors. "Markers of patients likely to respond to interferon are clearly needed, and this trial indicates that the combination of low tumour volume and an ulcerated primary tumour might be such a marker."

■ Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: final results of EORTC 18991, a randomised phase III trial. AMM Eggermont, S Suciu, M Santinami et al. *Lancet* 12 July 2008, 372:117–126

Post-mastectomy pain defined

➜ British Journal of Cancer

Nearly one quarter of women undergoing breast cancer surgery experience post-mastectomy pain syndrome (PMPS) one and a half years after their operation, according to a recent Danish study. The results showed that pain was more likely in women undergoing early surgery, those with tumours located in the upper lateral quarter and those who were young at the time of surgery.

PMPS, often located in the axilla, the shoulder, the arm or the chest wall, is frequently

described as a "typical neuropathic pain consisting of burning pain, shooting pain, pain evoked by pressure and deep blunt pain". In the current study, OJ Vilhom and colleagues from the department of Neurology, Odense University Hospital (Denmark) set out to estimate the current prevalence of PMPS and to identify risk factors. Questionnaires were mailed to 258 women, one and a half years after they had undergone surgery for breast cancer (either mastectomy or lumpectomy) at Odense University Hospital, with similar questionnaires being sent to a reference group of 774 women.

For the purposes of the study, PMPS was defined as pain located in the area of the surgery or ipsilateral arm that was present for at least four days per week, with an average intensity of at least 3 on a numeric scale from 0 to 10.

Results show that the prevalence of PMPS was 23.9% for breast cancer surgery patients compared to 10% for the reference population (OR 2.88; 95% CI 1.84–4.51).

Three risk factors were identified as significant for PMPS – having undergone breast surgery early (OR 8.12), tumour location in the upper lateral quarter (OR 6.48) and a young age at surgery (OR 1.04). Chemotherapy, axillary dissection, mastectomy, smoking, tumour size and radiation therapy were not associated with PMPS.

Although no differences in the description of pain were found between breast cancer patients and the reference group, the location of the pain differed, with breast cancer patients more likely to experience pain in the shoulder, the area of the scar, and in more than one location.

The majority of breast cancer patients with severe pain had pain located in the shoulder, axilla or arm. "This adds evidence to the finding of tumour located in the upper lateral quarter being an important risk factor, as operation in this area may tend to cause more nerve damage than surgery in other areas of the breast," write the authors.

"Although recent advances in diagnostic and surgical procedures have reduced the frequency of the more invasive surgical procedures, there is still a considerable risk of developing PMPS after treatment for breast cancer, and development of preventive measures as well as treatments of the syndrome are highly relevant," conclude the authors.

■ The post-mastectomy pain syndrome: an epidemiological study on the prevalence of chronic pain after surgery for breast cancer. OJ Vilholm, S Cold, L Rasmussen et al. *Br J Cancer* 12 August 2008, 99:604–610

Bisphosphonate prevents bone loss in pre-menopausal breast cancer

➜ Lancet Oncology

Using the bisphosphonate zoledronic acid in combination with adjuvant therapy (GnRH analogues and selective oestrogen receptor modulators) in premenopausal women following surgery for early breast cancer prevents bone loss, a sub-study analysis from the Austrian Breast and Colorectal Cancer Study Group trial 12 has concluded.

The ABCSG-12 study, by Michael Gnant, from the University of Vienna (Austria) and colleagues, aimed to compare tamoxifen versus anastrozole (an aromatase inhibitor) when added to goserelin-induced ovarian suppression as an adjuvant therapy in pre-menopausal, hormone-responsive early breast cancer.

A sub-study investigated the effects on bone mineral density (BMD) in both treatment arms, as well as the protective effect of concomitant bisphosphonate zoledronic acid.

In the study, 404 patients were randomly assigned to endocrine therapy alone (goserelin and anastrozole, or goserelin and tamoxifen, n=199) or to endocrine therapy concurrent with zoledronic acid (n=205). Zoledronic acid was delivered by seven intravenous infusions spaced over the three-year duration of the study. Lumbar spine and trochanter BMD measurements were made at baseline, 36 months and 60 months.

Results show after 36 months, the endocrine therapy alone arm had significant loss of BMD in comparison to baseline measurements at the lumbar spine (-11.3%, mean difference -0.119 g/cm^2; P<0.0001) and at the trochanter (-7.3%, mean difference -0.053 g/cm^2; P<0.0001). Patients who received zoledronic acid had stable BMD at 36 months, (+0.4%, mean difference 0.0004 g/cm^2 at the lumbar spine and +0.8%, mean difference 0.0006 g/cm^2 at the trochanter).

At 60 months (24 months after study completion), patients not receiving zoledronic acid still had decreased BMD at both sites compared with baseline (lumbar spine P=0.001, trochanter P=0.058) , while those receiving zoledronic acid still had increased BMD at both sites (lumbar spine P=0.02; trochanter P=0.07).

In the group randomised to no zoledronic acid, patients on anastrozole experienced greater BMD loss than those on tamoxifen at 36 months in the lumbar spine (P<0.0001).

Zoledronic acid combined with goserelin plus tamoxifen or anastrozole was generally well tolerated, with the only significant adverse events being bone pain (P=0.003), arthralgia (P=0.013) and fever (P=0.0001).

"Bone loss associated with adjuvant endocrine therapy in premenopausal women with early-stage breast cancer is of substantial clinical concern, because these women typically survive for many years after treatment," write the authors, adding that it will be interesting to monitor the long-term proportion of fractures, to establish whether substantial fracture prevention is associated with zoledronic acid therapy.

■ Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone mineral density substudy. M Gnant, B Mlineritsch, G Luschin-Ebengreuth et al. *Lancet Oncology* September 2008, 9:840–849

Promoting adherence to long-term hormonal therapy in breast cancer

➜ British Journal of Cancer

Women treated with long-term hormonal (endocrine) therapy are more likely to stick with the treatment if they are looked after in specialised oncology units than if they are

cared for by a family doctor, according to a major follow-up study.

Hormonal therapy has been recommended for the vast majority of postmenopausal women with hormone-receptor-positive breast cancer since the late 1990s. Expert guidelines recommend that elderly women with hormone-receptor-positive breast cancer take tamoxifen for five years. However, there are lots of reasons why it can be difficult for women to take hormonal therapy for such a long time. Previous research evaluating the use of adjuvant hormone therapy among post-menopausal breast cancer patients showed that between 15% and 50% women did not adhere to the treatment as recommended, with some women refusing even to start the treatment.

In the new study, a group of researchers from Basel, Switzerland, studied an unselected group of 325 postmenopausal women who were diagnosed with hormone-receptor-positive invasive breast cancer. They looked carefully at the different clinical situations that led to the women stopping their hormonal treatment, or not taking it exactly as recommended. Results showed that only 191 of the 287 patients (66.6%) who started hormonal therapy for five years completed this treatment.

Thirty-one patients (10.8%) chose independently to stop their hormonal therapy before the end of the recommended five years. The main reasons for non-adherence were general discomfort (29.0%), hot flushes (12.9%), skin symptoms and hair loss (9.7%), visual disturbance (3.2%) and alcohol dependency or psychiatric illness (9.7%). Just over one-third of these women did not give a reason for stopping their treatment. A further 8.9% of the women refused the recommended endocrine therapy after extensive counselling and never even began this treatment.

In the study, 25 patients changed their hormonal medication due to therapy-related adverse effects. Of these, 20 women (80%) completed their therapy after changing the drug they were prescribed.

Patients who had their follow-up care with a general practitioner were significantly more likely to be non-adherent than those looked after in an oncology unit (P=0.0088). Only one in ten (10.8%) of the women cared for by a specialised oncology unit did not take their hormonal therapy as recommended. The researchers concluded, "Our data show that, when compared with other studies, low non-adherence rates can be realistically achieved." They noted that this was probably associated with the fact that practitioners in specialist oncology units had received targeted education in patient-centred communication. "An important aspect of non-adherence is the ability of the physician to intervene and change the attitude that led to discontinuation."

■ Target and reality of adjuvant endocrine therapy in postmenopausal patients with invasive breast cancer. U Güth, DJ Huang, A Schötzau et al. *Br J Cancer* 29 July 2008, 99:428–433

Higher radiation levels show benefit in prostate cancer

➔ Int J Radiat Oncol Biol Phys

For prostate cancer, higher radiation dose levels are associated with significant improvements in long-term biochemical tumour control outcomes and reduction in the development of distant metastases, a US study has found.

Several randomised studies have already shown improved prostate-specific antigen (PSA) relapse-free survival outcomes for patients with favourable-, intermediate- and high-risk features who are treated with high doses of radiation in comparison to low doses.

In an earlier publication, Michael Zelefsky and colleagues from Memorial Sloan-Kettering Cancer Center (New York), reported improved biochemical outcomes when dose levels of 75 Gy and higher were used with three-dimensional conformal radiotherapy (3D-CRT). The current report presents a median follow-up of 6.6 years (range 3–18 years) of the same study.

A total of 2,047 patients with localised prostate cancer were treated with 3D-CRT or intensity-modulated radiotherapy (IMRT), with prescribed dose levels ranging from 66 to 86.4 Gy. Prior to radiotherapy, 990 patients (48%) were treated with short-course (three-month) androgen deprivation therapy (ADT) to decrease the size of their enlarged prostate prior to radiotherapy. Follow-up evaluations were performed at intervals of three to six months for five years, then yearly thereafter. Patients were classified into recurrence risk groups according to the National Comprehensive Cancer Network guidelines.

Results show that, for patients deemed to be at intermediate risk of recurrence, radiation dose was an important predictor for improved PSA relapse-free survival (P<0.0001), and improved distant-metastases-free survival (P=0.04). The beneficial effect was found to be most apparent between those receiving 75.6 Gy and more, compared with 70.2 Gy or less. Other variables, such as neoadjuvant ADT and age, were not significant predictors of biochemical control.

Higher dose levels were associated with improved biochemical outcomes in high-risk patients as well. Five-year PSA relapse-free survival outcomes for patients who received 86.4, 81, 75.6 and 70.2 Gy or less were 71%, 66%, 61% and 40% respectively.

"Taken together with other data, our findings confirm the underlying hypotheses and rationale for dose escalation in patients treated with clinically localised prostate cancer; namely that higher radiation doses improve local tumor control within the prostate, which in turn reduces the risk of distant metastases," write the authors.

The use of ADT was found to be a significant variable for improved biochemical control rates in high-risk patients, but not in intermediate-risk patients.

"It is possible that longer courses of ADT may further improve outcomes and reduce cancer-related deaths, even in the setting of higher radiation doses," write the authors, adding that only randomised trials will be able reliably to ascertain the role of hormonal therapy for patients receiving high-dose external beam radiotherapy.

■ Long-term results of conformal radiotherapy for prostate cancer: impact of dose escalation on biochemical tumor control and distant metastases-free survival outcomes. MJ Zelefsky, Y Yamada, Z Fuks et al. *Int J Radiat Oncol Biol Phys* 15 July 2008, 71:1028–1033

A diet of hopes and half-truths

Peter McIntyre

The media often hype the benefits of 'superfoods' to protect against or even cure cancer. But keeping weight down and taking exercise are known to offer far greater protection than any individual food or nutrient – however full of antioxidants it may be. How can health professionals support their patients to sort fact from fiction and make the necessary changes?

The health messages that bombard our daily lives are 'balanced' between scare stories and miracle cures. Mass media, the main source of knowledge for most people, often oversimplify research findings to the extent that they present exaggerated and misleading accounts.

Perhaps nowhere is this more so than in reports of the ability of 'superfoods' to protect us from disease, especially cancer. Recent claims have been made for the protective, or even healing, powers of kiwi fruit ("repair damage to our DNA"), mushrooms, oregano, potatoes ("inhibit tumour growth"), tea, cauliflower, tomatoes and vitamin C.

Good foods all of them – but none is an adequate shield against cancer, still less a substitute for treatment.

People who have been diagnosed with cancer often focus on diet and complementary therapies, because these seem to be more under their control than chemotherapy, radiotherapy or surgery, and because patients have a natural desire to do everything possible to try to get better.

But the public health messages that people receive from the media, and perhaps even from the 'five a day' campaigns to increase consumption of fruit and vegetables, run counter to what the latest research says about cancer and diet.

While alcohol and red meat have been linked to some cancers, the overall message is that body weight and levels of exercise are much more significant than individual foods. Diet is important, but the link between diet, exercise, body mass and cancer is complex and cannot easily be picked apart.

As Walter Willett, professor of Epidemiology and Nutrition at Harvard School of Public Health and leader of the Nurses' Health Study, described the current state of knowledge: "staying lean and active is the most important thing one can do to prevent cancer, after not smoking." And while he finds a modest cancer prevention benefit from eating more fruit and vegetables, "it's not the 'big bang' it was thought to be 15 or 20 years ago."

In 2007, the World Cancer Research Fund and the American Institute for Cancer Research put

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High risk or low risk? The five-a-day message has been heavily promoted, but the evidence shows it is diet as a whole rather than individual foods that matter – and exercise and keeping your weight down are crucial

being overweight as the number one risk for cancer after smoking (World Cancer Research Fund 2007). Their report found convincing evidence to link obesity to colorectal, endometrial, oesophageal, kidney, liver, pancreatic and postmenopausal breast cancer. Having a fat stomach and eating red and processed meat are risks for colorectal cancer, but evidence of the protective powers of individual foods was equivocal. Its recommendations put emphasis on exercise and weight reduction.

The dangers of being overweight after a diagnosis of cancer are significant. A study reported in *Cancer* (Wright et al., February 2007), found that severely obese men had twice the risk of death from prostate cancer after diagnosis, even though they were not at increased risk of developing prostate cancer in the first place.

The evidence on diet is not all negative. Studies in Greece, Italy, Sweden and the US have shown that a 'traditional Mediterranean diet' does substantially reduce the risk of cancer, and indeed a US study (Mitrou et al., *Arch Intern Med* 2007) found that those who followed a Mediterranean diet had lower mortality from any cause.

A recent study by Benetou et al. (*Br J Cancer* 2008), which followed more than 28,000 Greeks for eight years, showed a 12% lower incidence of cancer for those who were two points 'better' in terms of the Mediterranean diet. In other words, reducing the amount of meat in the diet and increasing the amount of peas, beans and lentils, or substantially increasing intake of vegetables and substituting olive oil for butter, can produce a 12% reduction in risk.

Dimitrios Trichopoulos, of the Harvard School of Public Health and the Hellenic Health Foundation, reports on the Greek study that is contributing to the Europe-wide EPIC study of cancer and nutrition in half a million Europeans. He emphasises the 'traditional' Mediterranean diet eaten from the time of the Ancient Greeks to the start of

Health messages people receive from the media run counter to what the latest research says about cancer

"The effects of diet should be looked at as an integrated entity, rather than as specific foods"

package holidays in the 1960s, not the diet in most of the Mediterranean region today.

The diet must also be seen as a whole. "Our philosophy is that essentially the effects of diet should be looked at as an integrated entity, rather than as specific foods. There have been several studies indicating that the Mediterranean diet is effective in increasing life expectancy, whereas individual food groups or food items seem to have little effect, if any."

Although his study may eventually track how those on different diets progress after a diagnosis of cancer, Trichopoulos says that it is difficult to separate dietary factors from the quality of treatment. "We have to recognise and make it clear that we don't really know if the factors that affect survival or metastatic-free survival are the same dietary factors that are relevant to the occurrence of cancer. Cancer has a very long natural history and perhaps different factors operate early on and later on."

Individual nutrients fail

What is clear is that attempts to package individual ingredients ('supernutrients') to protect against cancer have largely failed, and some have been disastrous.

In the 1990s, some people at high risk of lung cancer were given concentrated doses of beta carotene, an antioxidant found in carrots, spinach and broccoli. The ATBC Prevention Trial in Finland showed an 18% *increase* in lung cancer and an 8% increase in deaths in those who had taken beta carotene and vitamin E, while a parallel (CARET) trial in the US was even worse – 28% more lung cancers and 17% more deaths in those who took beta carotene with vitamin A.

In 2007, an American study to test whether folic acid, found in green vegetables and potatoes, could prevent early-stage colon cancer instead found a slightly higher rate of colorectal adenomas (such as polyps) in the test group, leading to higher rates of the advanced lesions that lead to colorectal cancer.

A 2007 study of 28,000 men in the US did not find that lycopene (the 'wonderfood' in tomatoes) offered protection against prostate cancer.

Claims made for vitamin C as either a preventative or a cure for cancer remain unsubstantiated.

Breast cancer and diet

One of the most puzzling areas of study has been on the role of diet in women who have been diagnosed with breast cancer. Two large and well-respected studies appear to contradict each other.

The WINS study reported in December 2006 on 2,437 women who had been treated for early-stage breast cancer and randomised to a lower-fat or their usual diet (Chlebowski et al., *JNCI* 2006). At the end of five years, breast cancer returned in 9.8% of women on the low-fat diet, against 12.4% in the control group – a 24% reduction in risk. The following year, the Women's Healthy Eating and Living

The traditional Mediterranean diet

The Greek study measures a traditional Mediterranean diet by nine factors:

1. The ratio of mono-unsaturated fats (as in olive oil) to saturated fats (as in red meat and biscuits)
2–5. High levels of fruit, vegetables, legumes and unrefined cereals
6. Moderate to high levels of fish
7. Low levels of meat
8. Low to moderate consumption of dairy products
9. Moderate consumption of ethanol (in wine)

(WHEL) study (Pierce et al., *JAMA* 2007) came up with opposite results. After four years, there was virtually no difference in the rate of metastases in women on a low fat/high vegetable, fruit and fibre diet, compared with women in the control group.

Perhaps one critical difference was that in the WIN study the diet group experienced significant weight loss, while in the 2007 WHEL study both the diet and control group experienced small weight gains. It is also significant that an earlier WHEL study showed that women who had been treated for breast cancer and who combined exercise (six half-hour walks a week) with a healthy diet (five servings of fruit and vegetables a day) halved their mortality rate compared to other women.

The Diana study recommendations

This is the advice given by the Franco Berrino's team at the National Cancer Institute in Milan to women who have been diagnosed with breast cancer:

1. Reduce calorie intake, by choosing filling foods such as unrefined cereals, legumes, and vegetables
2. Reduce high glycaemic index and high insulinaemic index foods, such as refined flours, potatoes, white rice, cornflakes, sugar and milk, and use instead wholegrain cereals (unrefined rice, barley, millet, oat, buckwheat, spelt, quinoa), legumes (including soya) and vegetables (except potatoes)
3. Reduce saturated fat (in red and processed meat, milk and dairy products), using instead vegetable fats such as olive oil, nuts and seeds
4. Reduce protein intake, especially animal proteins (except fish)

Diet, weight and waist size

Franco Berrino and his team at the National Cancer Institute in Milan say that overweight and obesity can be key factors in hormonal breast cancer after menopause (*Ann NY Acad Sci*, 2006). At greatest risk, says Berrino, are women who have metabolic syndrome – in other words any three of the following: low good cholesterol, high triglycerides, high glucose levels, high blood pressure and large waist circumference. "In short, sedentary lifestyle, overweight and a fat-rich diet are major determinants of metabolic syndrome which in turn is associated with insulin resistance and increased androgenic activity."

Berrino has shown in two (smallish) studies of Italian women (the Diana studies) that a Mediterranean and macrobiotic diet can reduce body weight, metabolic syndrome and the bioavailability of sex hormones and growth factors. A group of 104 healthy women showed decreases of 29% and 23% in the amount of free testosterone and free oestradiol in their blood after five months of eating recommended foods. A study of 110 breast cancer patients showed reductions of 10% in testosterone and 6% in oestradiol after a year on the diet.

Knowing what changes to make is one thing – making them is another. In the first Diana study, the women lost an average of 4 kg each with support from the Milan team.

"We never talk to these women about counting calories," says Berrino. "The recommendation was: eat as much as you desire, but eat only this type of food, which is highly satiating. The strategy is to eat only low-calorie-dense food. No drink containing sugar. No flour made with refined wheat or potatoes, which are very high on the glycaemia index."

The next study (Diana 5) of both diet and exercise will involve 2,000 Italian breast cancer patients who have either metabolic syndrome or high levels of testosterone or insulin in the blood. Berrino says that, whereas in the small trials they were able to give women support to stay on the diet, in the large trial it will prove difficult, especially if a husband or children do not want changes in the diet at home. "The world now behaves in a different way," says Berrino. "If you go to a restaurant, it is difficult to find what we recommend."

One problem is that people do not report everything they eat. Berrino says, "If you look at studies of this kind and you compute how many kilograms

"It could be especially difficult if a husband or children do not want changes in the diet at home"

WORLD CANCER RESEARCH FUND RECOMMENDATIONS

1. Be as lean as possible without becoming underweight
2. Be physically active for at least 30 minutes every day. Any type of activity counts – try to build some into your everyday life
3. Avoid sugary drinks. Limit consumption of energy-dense foods, particularly fast foods and processed foods high in added sugar, low in fibre or high in fat
4. Eat a greater variety of vegetables, fruits, wholegrains and pulses such as beans. As well as five a day of fruit and vegetables, try to include wholegrains like brown rice, wholemeal bread and pasta and/or pulses with every meal
5. Limit consumption of red meat (beef, pork and lamb) and avoid processed meats
6. Limit alcoholic drinks (if any) to two a day for men and one a day for women
7. Limit consumption of salty foods and food processed with salt
8. Don't use supplements to protect against cancer (supplements may be advisable for other reasons)
9. It's best for mothers to breastfeed exclusively for up to six months
10. After treatment, cancer survivors should follow the recommendations for cancer prevention. The Report found growing evidence that maintaining a healthy weight through diet and physical activity may help to reduce the risk of cancer recurrence. All cancer survivors should receive nutritional care from an appropriately trained professional

they should have lost if what they declare is true, they have lost perhaps two kilograms, and they should have lost 20! It is funny, but it is not cheating. It is just the psychological aspect; you declare what you should eat not what you do eat. For measuring compliance, you must use objective studies, scales, cardio respiratory fitness and so on."

How do you make changes?

Heather Bryant, chair of the Institute of Cancer Research Advisory Board, at the Toronto Sunnybrook Regional Cancer Center in Canada, warned at the World Cancer Congress in Geneva that people find it hard to act on dietary advice. What is a healthy diet? What is red meat? Her team encourages people to use their mobile phones to take pictures of what they eat, so they can show their dietician what a portion means to them and what they are actually eating. "Just because people buy something does not mean that they eat it. The amount of broccoli in landfill has increased in recent years!"

She summarises the key messages as: "Be as lean as possible within a normal range," and "limit energy-dense and sugary foods and drinks." People should be given specific advice – increase fruit and vegetables, decrease fat – rather than being told to eat a healthy diet.

Steve Pratt, a dietician and exercise physiologist with the Cancer Council in Western Australia, says that many patients need individual advice while undergoing treatment. "There are a lot of cancer patients for whom the message is the same healthy eating message you give the rest of the population: plenty of fruit and vegetables, plenty of plant-based foods. Other cancer patients need much more individualised clinical advice.

"There will be people who have relatively trouble-free treatment and a transition into survivorship in which we hope they adopt a healthy lifestyle. Others get knocked around by treatment and will have the nausea, fatigue and the loss of appetite that can accompany radiation therapy and chemotherapy.

"For many people, however, particularly those treated for breast or prostate cancer, one of the big concerns is weight gain. The drugs that are commonly used in the treatment of those two conditions interfere with hormone metabolism, and can actually lead to quite significant weight gain, compounded by feelings of fatigue. It can be a vicious cycle. The key is to break it somehow.

"Patients are asking for advice on these genuine and legitimate concerns. But diet and exercise fall between the cracks in the treatment world, though they do have an evidence base and are legitimate adjuvant therapies."

People need support as well as advice. "It is hard to make long-term changes. People often revert to their original lifestyle habits, whether diet or exercise."

"Patients are asking for advice. But diet and exercise fall between the cracks in the treatment world"