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Education & knowledge through people & facts

Alain Fourquet

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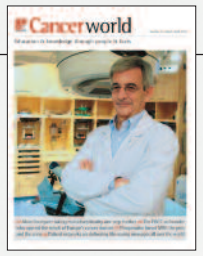

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Stop excluding male patients

Fatima Cardoso ■ GUEST EDITOR

Male breast cancer is a rare disease, accounting for less than 1% of all breast cancers worldwide. According to the American Cancer Society, last year it was expected that around 1910 men would be diagnosed with breast cancer in the US with around 440 deaths, compared with around 192,370 expected new cases and 40,170 deaths among women.

Male breast cancer patients go through their difficult fight with very little support, while having to cope with the additional stigma of having a 'female disease'. They also suffer from a lack of evidence on how best to manage their disease. Not a single randomised phase III trial has ever been concluded on male breast cancer. As a consequence, management of male breast cancer is mainly done by extrapolation from its female counterpart.

The Breast International Group and the North American Breast Cancer Groups have now joined forces to launch a three-part international research programme for male breast cancer, coordinated by the EORTC. It has kicked off with a meta-analysis of clinical data and a central pathology review of tumour specimens from about 1700 male breast cancer cases diagnosed in participating institutions over the last 20 years. Part 2 of the programme will involve building a prospective international registry of all male breast cancer cases diagnosed at participating institutions over a two-year period, to collect data on demographics, risk factors, treatment and outcomes. Funding is being sought to finance a central analysis of the biological material collected, with a virtual tumour bank being used in the meantime.

The intention is to proceed to a randomised clinical trial of endocrine therapy, which could be launched as part 3 of this programme. In view of the failure of all previous attempts to run a clinical trial in this setting, a fully committed international effort will be indispensable.

Securing funding for such a non-drug related, purely academic effort has been a daunting process, demonstrating once again the need for a central funding body in Europe. While continuing to look for additional sources of funding, work on the retrospective analysis has already begun thanks to support from the US Breast Cancer Research Foundation.

This research programme could greatly enhance our knowledge of the biology of male breast cancer – an essential first step to guide the development of future therapies. While waiting for the results, a plea is made to all those involved in the design and implementation of breast cancer trials to stop excluding male patients without a good reason. If excluding male patients from endocrine therapy trials may be understandable, excluding them from trials of cytotoxic and biological agents is not. Cancer societies and organisations also need to play their part, by increasing efforts to raise awareness and establish support groups for these patients.

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Alain Fourquet:

taking multidisciplinarity one step further

➜ Marc Beishon

Alain Fourquet will break new ground this March when he becomes the first radiation oncologist to chair Europe's major breast cancer conference, EBCC 7. He believes progress is being hampered by tunnel-vision drug trials, with protocols that are blind to the effect that the compounds, and the timing of their delivery, have on the patients' sensitivity to radiotherapy and the toxicity of the overall treatment. Delegates can expect to hear a call for radio-oncologists to be involved at an earlier stage.

The importance of a truly multidisciplinary approach to cancer care, though almost universally acknowledged, has yet to be realised in practice outside of the top cancer hospitals. Lack of resources, industry influence, fragmented hospital departments and ascendancy of certain personalities and specialisms – all these play a role in stalling progress. And all are especially apparent in Alain Fourquet's specialty, radiation oncology, which despite being one of the three central pillars of cancer treatment is often relegated to last place behind medical oncology and surgery.

As Fourquet, head of radiation oncology and a specialist in breast cancer and breast conservation at the Curie Institute in Paris notes, it is not just the shortage in many countries of equipment and specialists such as medical physicists and radiographers that accounts for poor recognition of the role of radiation oncology. "One problem is that people are understandably excited about new targeted drugs, but in some of the major trials we are seeing treatments applied without any real evidence of what order and for how long we should be doing things, such as when to give adjuvant chemotherapy and radiotherapy and how to determine efficacy and toxicity. People tend to lack knowledge and expertise in treatments outside their own specialism," he says.

"Another good example is the trend to implement partial breast irradiation in some countries, such as the US. We don't know whether it is effective – there is no proper science behind it. The history of cancer treatment and breast cancer in particular is that you cannot decide quickly on the effectiveness of new treatments – it can lead to much frustration and misleading conclusions." And failure to integrate insight and expertise across the disciplines is behind much of the rush to premature judgements, he adds.

Fourquet speaks with the authority of virtually an entire career spent in breast radiation oncology, and

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with an immense knowledge base on some of the oldest – and tried and tested – techniques. "We know that adjuvant radiotherapy cuts the risk of recurrence of breast cancer by 70%–75%. There are no drugs that do that," he says.

Certainly, if there is one place in Europe where a supportive culture of all disciplines, and radiotherapy in particular, is apparent, it is the Curie Institute – founded by one of the most famous scientists, radiation pioneer Marie Curie, and a clinician, Claudius Regaud.

"Of course, radiotherapy along with surgery were for many years the only options for treating cancer before we had chemotherapy," says Fourquet. "But the Curie and France overall has a particular heritage in using radiation in breast conserving treatment, which actually goes back to the 1950s. When I came here it was standard treatment, but unusual elsewhere. It has been routine in French centres since the early 1970s – and wasn't recommended in the US until the end of the 1980s."

Fourquet's contribution to the field can best be described as steady, if not spectacular, in line with his belief in the importance of applying research over the long term to understand properly the mechanisms involved in certain approaches. Implementing radiotherapy techniques in general has also been a major preoccupation in recent years. With colleagues at the Curie, he has been patiently building up

"Adjuvant radiotherapy cuts the recurrence of breast cancer by 70%–75%. There are no drugs that do that"

"I think we have the tools now to identify targets not only for drugs but for radiotherapy too"

optimal radiation treatment regimens for breast cancer, and now, as department head for all cancer types, he has been bringing in the new technologies that have radically changed radiotherapy – but doing so with caution and a heavy emphasis on training.

In addition to clinical work, Fourquet has been instrumental in driving clinical and translational research at the Curie, which is also France's largest cancer research institute as well as being a comprehensive cancer centre with its own hospital (in fact it has two hospitals now, following a recent merger with Centre René Huguenin, another cancer centre in Paris). "The future clearly lies in gaining a much better understanding of the biology of breast cancer and other tumours, and I think we have the tools now to identify targets not only for drugs but for radiotherapy too."

A case in point is work being carried out by one of his PhD students on genetic profiling of younger women with breast cancer – why they have a higher recurrence rate and the response to radiotherapy. "This is something I've had in mind for some time, and was started by my student with colleagues at the National Cancer Institute in Amsterdam, and is continuing here, as we have a large genomic platform. More results will be presented at the European Breast Cancer Conference [EBCC]."

Fourquet has a vested interest in publicising the

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EBCC – he is the chair of this year's event, although he is not one of Europe's great meeting attendees. He tends to pick and choose where he travels, and elected not to go to the San Antonio breast meeting last year, for example. "I agreed to take on the EBCC for two reasons. First, it is becoming an important European conference and we need to have events like this here. I don't see it competing with the US and it has a wider multidisciplinary emphasis. And second, as far as I know, there has not been a radiation oncologist in the chair until now."

With colleagues, Fourquet has shortened the conference to three and a half days – it was too long before, he says – and he is injecting more practical debate on clinical cases and controversies, along with the traditional coverage of both clinical and research topics across the breast cancer spectrum. "We have kept the format of parallel sessions and coverage of organisational and political issues as well. Of course we need to balance all interests, with the conference being jointly organised by Europa Donna [European Breast Cancer Coalition], EUSOMA [European Society of Breast Cancer Specialists] and the EORTC (European Organisation for Research and Treatment of Cancer]."

As for the profile of radiation oncology at this year's EBCC, it's no accident that among a good showing for the field the keynote Emmanuel van der Schueren lecture will be on 'Research progress and priorities in breast radiotherapy,' to be delivered by John Yarnold, a clinical oncologist at the Royal Marsden in London.

Fourquet knew he wanted to be a doctor from an early age, and went to medical school in Paris. But like many, his choice of specialism came by chance. "I was interested in oncology and haematology, and an opportunity came to work at the Curie, where the director was then Robert Calle, one of the pioneers of breast conservation." He obtained a resident's post and has never really looked back.

Although some other cancer sites formed parts of his early work, such as lymphomas and Hodgkin's disease, he moved rapidly into breast, becoming head of the radiation oncology breast cancer service by 1991, and chairman of the entire department by 2006.

"I did though spend a year on a fellowship at the Memorial Sloan-Kettering in New York, working with Samuel Hellman, who was one of the first in the US to report breast conserving treatment. I was very close to him. He is a great physician and a dedicated scientist, and was an example for many of my generation. He encouraged me to build up a long-term research programme, which we have done."

But it has not been easy to build up translational research, in particular. "It wasn't very popular with the biologists here at first, but we now have several translational programmes in my field." The Curie Institute is now the largest cancer research centre in France, working to an international level in many fields. Recent additions include a developmental biology and cancer centre, opened in 2008.

The Curie, he adds, has been rather slow to publicise its achievements and scale – most in the cancer community would cite the Gustave Roussy Institute in the Paris suburb of Villejuif as France's premier cancer centre. "They have been more active with their PR – but we will be launching a new website this year with a special breast cancer focus that will highlight our achievements and facilities much better," he says.

Apart from the main research and hospital location in central Paris, the Curie also has labs in the suburb of Orsay, and based there is one of only two proton therapy machines in France (the other is in Nice). "Then with the merger with Centre René Huguenin we will go up to 3000 breast cancer patients a year, from 1700," says Fourquet, "and we aim to have one in five patients for all tumours in clinical trials."

It is a substantial operation, and he also emphasises that the Curie has not only some of the most modern treatment technologies and research platforms, but also the databases and experience, in breast cancer in particular, going back decades, which are proving valuable for research.

One key finding has been fundamental to promoting the benefits of radiotherapy. "We have been able to demonstrate that radiation for breast cancer

"I don't see EBCC competing with the US, and it has a wider multidisciplinary emphasis"

not only has an impact on local control and helps preserve the breast in good condition, but also has an impact on survival, independent of other treatments, which has come recently from statistical overviews such as that by the Oxford Group under Richard Peto. Properly doing our radiation treatment has a secondary impact on distant metastases and cuts long-term mortality."

As he adds, "We were not able to show this for a long time, because the way radiotherapy was delivered 20 to 30 years ago introduced sequelae and long-term complications, and even radiation-related mortality. That's not the case anymore – we can spare the toxicity and see the long-term impact. Here, we now offer radiotherapy to 85% of women operated on for breast cancer, which is not the case everywhere, although that's partly due to lack of access to facilities."

That radiotherapy technology has moved on recently is an understatement. As Fourquet notes, the key linear accelerator (linac) machines have not only become much smaller and more reliable, but also radically improved with techniques such as IMRT (intensity-modulated radiotherapy) and integration with sophisticated imaging. "The machines we use now can provide different photon energies for varying the dose, and the combination of imaging and IMRT means that rather than giving a homogeneous dose to one region we can adapt to the anatomy or shape of a tumour. The first big step was 3D conformational targeting and also being able to measure the actual dose in a [tumour] volume and organs at risk, which we couldn't do before."

The Curie, he adds, was one of the first in Europe to install a tomotherapy machine, which has a CT scanner and linac built into a circular head and allows modulated doses to be delivered at any angle, with the patient on a moving table. "We can really focus treatment on complicated volumes with this, such as being able to spare salivary glands almost completely when treating head and neck cancer – it's better than what is now conventional IMRT."

He stresses, though, that the aim is to have a 'one stop shop' for all radiotherapy options – simple machines are fine for some treatments, such as skin cancer – and with the proton facility and a large number of different machines at the main institute (there are seven linac suites alone), he feels this aim will be achieved with the delivery of a new proton machine, expected this April, which will replace an outdated unit. "In patients with melanoma of the eye, we can achieve about 95% local control with protons. We are aiming especially to treat more children with proton therapy, which will help to cut the long-term risk of contracting other cancers later in life."

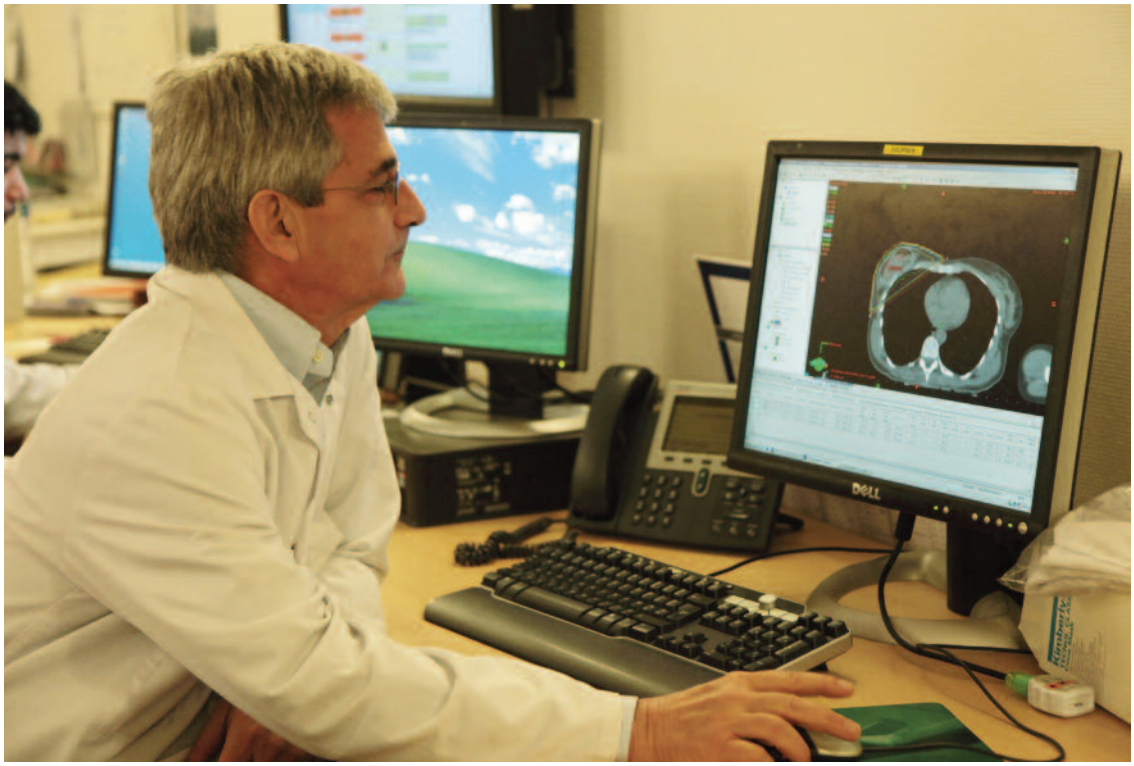
A major problem is the sheer complexity of the new technologies. "It has been like moving from a single-seater plane to an Airbus – we have many more controls and verification systems, as sources of error are now everywhere. It's very demanding in terms of training and awareness and we have to be extremely cautious."

Fourquet has a small army of physicists, dosimetrists, radiographers and so on in his large department – the simulation and set-up involved in preparing and delivering treatment is very labour intensive and requires extensive knowledge, despite the fact that it is all done on computers. He is mindful that France, like most countries, has had disastrous failures with radiotherapy — as recently as 2007 there was a major scandal when it was revealed that a hospital in Epinal, north east France, had overdosed many patients, some of whom died.

"That was a good example of many things you should not do," says Fourquet. "The second French cancer plan, which was issued recently, addresses quality in radiotherapy with more radiation oncologists and medical physicists, and a minimum number of patients that a centre must see. It also focuses much more on multidisciplinary working and translational research. To my mind it is much better than the first plan, although that did generate investment in more modern facilities across the country."

The new criteria for radiotherapy units include a minimum of 600 patients a year, with two machines in operation to increase 'up time'. "You cannot have a centre with only one machine any more, which may cause

"We aim to treat more children with proton therapy, which will cut the risk of other cancers later in life"



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"It has been like moving from a single-seater plane to an Airbus... sources of error are now everywhere"

us problems with capacity. We also have big discussions here about whether we should move to publishing outcomes of hospitals as well, as the UK is doing."

The application of radiotherapy in breast cancer has meant applying evidence-based research to counter dogma over the years, says Fourquet, so any new research focus in France's cancer plan is only to the good. The demonstration of a mortality impact after controlling for factors such as cardiac mortality has itself helped dispel the dogma that came with the chemotherapy era – that breast cancer was metastatic and local treatment could have no impact. "The quality of local treatment actually then declined until we could show its survival impact," he notes.

"We also published one of the first papers on conserving treatment for DCIS [ductal carcinoma in situ – non-invasive cancer]. Back then there was dogma that DCIS was radio-resistant so the whole breast should be removed. We started a prospective database, which now has 30,000 files, and by 1989 we were able to show that treatment with conserving surgery and radiation has a similar rate of recurrence as with invasive cancer. This triggered a lot of studies to understand DCIS."

Then there is ongoing work on younger women at high risk of cancer through the genetic *BRCA1/2* mutations. It had been thought that mastectomy is necessary because conserving surgery followed by radiation would be detrimental because of a lack of DNA repair genes, and cancer may be induced. "But we have been able to show, with others, that there are no more recurrences than in those without the mutations. The explanation seems to be that, although these aggressive tumours lack the ability to

"You could make a small gain by adding a chemo cycle and lose it by delaying radiotherapy,"

repair the DNA mutations, they are actually more sensitive to radiation. This is ongoing research and we need more data, but we have good clues now." Another major study, carried out by Fourquet and colleagues in the EORTC, has shown the benefit of a higher 'boost' radiation dose for younger women, and is also the subject of more ongoing trials in France and the Netherlands.

At the other end of the age spectrum, he is equally sure that older women deserve the opportunity to have a full range of treatment, including radiotherapy and chemotherapy, provided health assessments show they can tolerate it. "When the UK, for example, decided not to treat women just because they were old back in the 1970s and 80s, the outcomes were terrible. We nearly always offer radiotherapy to older women here, as we know we can also spare the heart and lung, and we have particular regimens for frail patients."

Some oncologists are suggesting now that older women do not need radiotherapy, but as Fourquet points out, "With the benefit of cutting the risk of recurrence by 70%–75%, what threshold do you decide this is useless for any group? Yes, there could be a patient for whom you estimate the risk is 1% over 10 years, so I agree, a drop to 0.3% or so is tiny. But that is not most patients – the only group I can think of are women who have surgery and endocrine treatment – and then the question is: Which is better, a few courses of non-toxic radiotherapy or five or more years of endocrine drugs with potential side-effects?"

A trend he is particularly concerned about now is partial breast irradiation. "The idea of treating only part of the breast with radiation came about for a good reason in states such as Louisiana and Texas in the US where access to health facilities can be poor and women often cannot afford to travel long distances for several radiation cycles. Rather than carrying out mastectomies, oncologists wondered if they could preserve the breast and cut the number of radiation cycles." The first studies with techniques such as brachytherapy (implanted radiation sources) were interesting, he says, and industry then stepped in with many more approaches. In Europe, countries with overstretched radiotherapy units also became interested, in particular the UK, Italy and Hungary.

"But we don't know if it is effective – there is no real science behind the idea of irradiating a smaller volume. There are trials running now that will eventually give an answer, but not after five years, as most recurrences by then are in the initial site. By ten years and beyond we will see if there are differences. What we know from trials such as that carried out by

Umberto Veronesi on conserving surgery alone against surgery and whole breast irradiation is that you have three to four times the number of recurrences if you don't do radiotherapy, and we know in the longer term we see recurrences elsewhere in the breast, even clonal recurrences – the same as the original tumour – far from the initial site."

As he adds, the trials must go on. "But the approach goes against what we have learned about breast cancer – the host, genetic predisposition and precancerous lesions make up the background for developing the disease and the effect of radiation on the whole organ is why it works. There is no logic to applying a small volume of radiation just because you can."

Where multidisciplinarity is becoming especially important now is in untangling the impact of the many combinations of treatment options opening up with targeted agents. The problem is, says Fourquet, that there is sometimes scant regard for designing trials that demonstrate the efficacy/toxicity balance. "In the conventional surgery, chemotherapy, radiotherapy sequence, there can be trials to insert more cycles of chemotherapy, each time postponing radiotherapy, despite the fact we have shown that the interval between surgery and radiotherapy may have an impact on local control. You could make a small gain by adding a chemo cycle and lose it by delaying radiotherapy, and the patients get more treatment for no benefit." Resources such as Adjuvant! Online also make no mention of radiotherapy, he notes.

Things get more complex with the addition of agents such as Herceptin (trastuzumab), which can improve adjuvant chemotherapy in 20% of patients. "In the first trials it was given differently – in Europe in the large HERA trial it was started after the end of all therapy, including radiotherapy. But in the US, it was started with chemotherapy and continued during radiotherapy – but it was not tested, just decided. Herceptin is known to improve the radiosensitive effect *in vitro*, the same type of effect we see with anthracyclines and other drugs. It also has potential cardiotoxicity, so giving it at the same time as radiotherapy raises concerns about long-term harm, but this was not tested in any trial.

"This is a typical example with new agents – angiogenesis inhibitors such as bevacizumab [Avastin] can be similarly toxic with radiotherapy. We need to be involved to test new compounds for both toxicity and efficacy by coordinating trial design with medical oncologists and industry. It's too late when the trials are running."

With breast cancer 10-year survival rates up to 85%, and local recurrence at 6% over the same time, it is of course the groups who have high recurrence rates that most concern Fourquet and colleagues, and the need to avoid unnecessary treatment to others. Like many radiation oncologists, he can see the potential to evolve the field into guiding radiation by tumour biology rather than just conventional imaging. "We need to be able to predict the radiosensitivity of tumours, knowing how various subtypes express genes involved in DNA repair. We can also expect to modulate the way we give radiation according to the structure of the tumour, where we could vary treatment depending on which part of it is growing, using functional imaging such as PET. We are already using PET to target volumes in Hodgkin's disease that spares other tissues. But we need more backing for research into radiobiology and experimental radiotherapy."

Expect many of these themes to be aired at the EBCC, and for radiation oncologists to be pretty visible, such as one of Fourquet's most well-known and closest colleagues, Harry Bartelink, long the radiation expert at the Amsterdam National Cancer Institute.

Fourquet's wife Nicole is also in medicine, working as a health geographer, and they have three children, one of whom is a biologist, and one grandchild. That no doubt sparks conversation about his main aim – to drive techniques such as gene profiling forward into everyday guidance for radiation. That's ambition enough he feels, and in any case he can see no reason to leave France's premier cancer institute. And with Marie Curie's laboratory preserved in a small museum on the site, there is certainly motivation to build on her legacy.

"We must coordinate trial design with medical oncologists and industry. It's too late when the trials are running"

Neutropenia in cancer patients: risk factors and management

Neutropenia – low levels of neutrophils – poses a serious threat to patients on chemotherapy. It exposes them to the risk of infection – including potentially fatal infections – and also leads to delays in treatment and reductions in dose intensity, which can compromise the chance of a favourable outcome. Awareness of risk factors and prompt action are essential.

Severe neutropenia places patients at high risk of serious infection. The lower limit of normal blood neutrophil count is approximately 2000/mm^3. Counts below this are classified as neutropenia, and graded according to severity. Counts below 500 cells/mm^3 are categorised as grade 4, between 500 and 1000 as grade 3, between 1000 and 1500 grade 2, and the least severe – between 1500 and 2000 cells/mm^3 – grade 1.

Neutropenia increases susceptibility to infection, particularly in cancer patients. We have known since the early 1960s that both duration and severity of neutropenia are factors that lead to febrile neutropenia – fever and infection – in cancer patients. The duration of neutropenia is particularly important in terms of the risk of infections.

Some key lessons in the management of febrile neutropenia in cancer patients have been learned since the 1960s. We have learned to anticipate the problem, and to see and evaluate our patients promptly when any sign of an infection occurs. We have learned

European School of Oncology
e-grandround

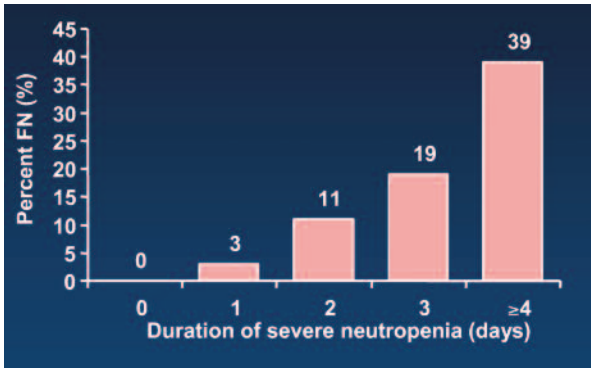
The European School of Oncology presents weekly e-grandrounds which offer participants the opportunity to discuss a range of cutting-edge issues, from controversial areas and the latest scientific developments to challenging clinical cases, with leading experts in the field. One of these will be selected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

In this issue, David Dale, of the University of Washington, in Seattle, USA, reviews the risk factors associated with neutropenia in cancer patients treated with chemotherapy, together with management strategies to reduce adverse outcomes.

Jeffrey Crawford, of the Duke University Medical Center, in Durham, North Carolina, USA, poses questions that explore the issue further. The presentation is summarised by Susan Mayor.

The recorded version of this and other e-grandrounds, together with 15 minutes of discussion, is available at www.e-eso.net/home.do

PROMPT TREATMENT IS KEY



The risk of febrile neutropenia (FN) rises steeply in cancer patients the longer severe neutropenia persists unchecked

Source: Adapted from Luiz Meza et al. *Proc Am Soc Clin Oncol* 2002; 21: abstract 2640

where to examine the patient, looking particularly at the skin, the mouth, the area around the anus, and the abdomen for signs of infection. A complete blood count should be taken, including white blood cell count (WBC), WBC differential, haemoglobin, haematocrit and platelet count. If there is fever and severe neutropenia, it is essential to start antibiotics promptly. These basic clinical practices are extremely important for the welfare of our patients.

For the past few years, I have been working with my colleagues in the ANC (Awareness of Neutropenia in Chemotherapy) study group towards defining as precisely as possible the risk factors associated with infection, fever, reduction in chemotherapy and unfavourable outcomes in cancer treatment. Or, looked at from another perspective, we have been working to identify the factors that lead to a favourable outcome.

Risk factors

Most clinicians who have been in practice for a long time will have had experiences of patients doing unexpectedly poorly or dying early in cancer treatment. This risk heightens concern about providing good care and emphasises the need to know the landmarks along the way to avoid this very unfavourable outcome.

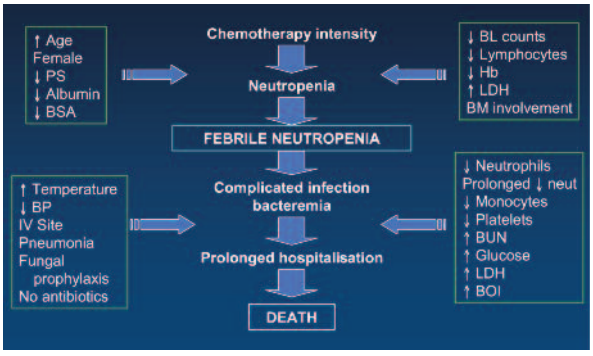
The figure below outlines the factors that are associated with neutropenia in cancer patients as well as the prognostic factors or risk factors for unfavourable outcomes in patients receiving chemotherapy.

One of the most important findings made by the ANC study group a few years ago is that the greatest risk of febrile neutropenia in a patient receiving a course of chemotherapy is with the first cycle. The figure opposite (*top*) shows the hazard ratio or risk of febrile neutropenia in patients with non-Hodgkin's lymphoma receiving standard-dose CHOP (cyclophosphamide, adriamycin, vincrinstine and prednisolone) or equivalent chemotherapy. There is a major peak of febrile neutropenia occurring about 10 days into treatment – at the time of maximum neutropenia with these standard drugs. Later cycles tend to be associated with less severe risk of febrile neutropenia.

Many factors may account for this observation, including dose reductions and adaptation of the haematopoietic system after an episode of neutropenia. It is important to realise that neutropenia is a predictable result of exposing the haematopoietic system to standard myelotoxic chemotherapy drugs. This pattern of febrile neutropenia peaking in the first cycle of treatment is observed across a wide spectrum of different types of cancer, indicating that it is a general pattern and that great vigilance is required with the first cycle of treatment with myelotoxic agents in all types of cancer.

In the course of our research, we looked at risk factors for neutropenia. The figure opposite (*bottom*) shows important and common risk factors, identified using a risk model based on 1246 patients with non-Hodgkin's lymphoma who were receiving CHOP. The easily identified risk factors, shown here for patients with lymphoma but more generally applicable, are: age, albumin (as a proxy for nutritional status), the intensity of chemotherapy, the starting white blood cell or neutrophil count, and the presence of hepatic disease. The more risk factors, the greater the risk. Being aware of

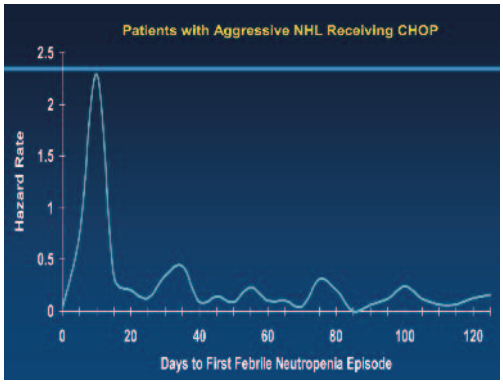
RISK FACTORS AND COMPLICATIONS



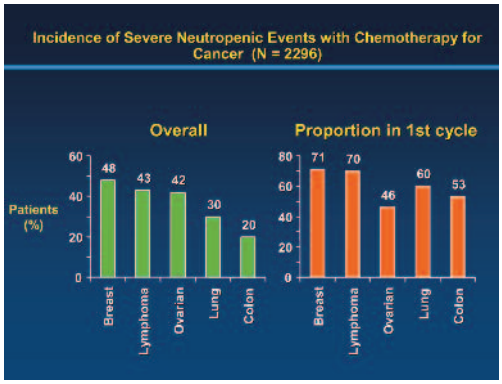
Knowing what to look out for is key to avoiding the worst outcomes

PS, performance status; BSA, body surface area; BP, blood pressure; BL counts, blood leukocyte counts; Hb, haemoglobin; LDH, lactate dehydrogenase; BUN, blood urea nitrogen; BOI, burden of illness; *Source:* GH Lyman *The Oncologist* 2005; 10:427-437. Reproduced with permission of ALPHAMED PRESS

THE FIRST CYCLE CARRIES THE HIGHEST RISK



The greatest risk for febrile neutropenia comes 10 days after the start of chemotherapy in patients with aggressive non-Hodgkin's disease



In patients with the five most common cancers, the majority of severe neutropenic episodes (between 53% and 71%) occur with the first cycle

Source (left): Lyman GH, Morrison VA, Dale DC et al. Risk of febrile neutropenia among patients with intermediate grade non-Hodgkin's lymphoma receiving CHOP chemotherapy. *Leukemia and Lymphoma* 2003, reprinted by permission of the publisher (Taylor & Francis Group, http://www.informaworld.ocm)

Source (right): Adapted from J Crawford et al. *J Natl Compr Canc Netw* 2008; 6:109–118

these risk factors helps health professionals to anticipate the problem of febrile neutropenia.

Multivariate analysis shows that age is a very important risk factor, and all older cancer patients need to be aware that they are at greater risk of febrile neutropenia when starting chemotherapy, usually not just because of their age but also because of the comorbidities that accompany the ageing process.

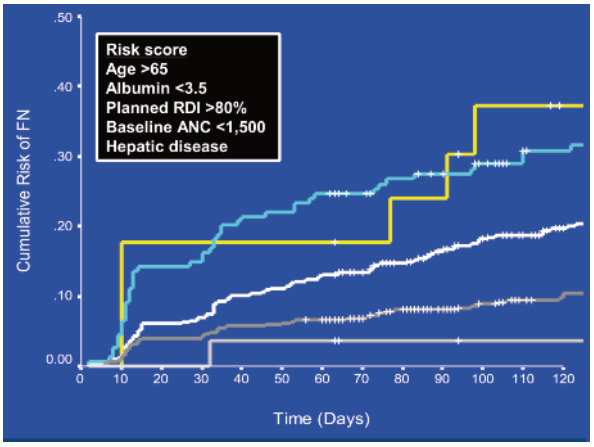
MORTALITY, MORBIDITY AND COSTS

Patients who have febrile neutropenia that makes them sick enough to be admitted to hospital have a high risk of an unfavourable outcome. A study by Kuderer et al, which looked at more than 40,000 adult cancer patients treated in large US hospitals, found a mortality rate of 9.5% (*Cancer* 2006, 106:2258). This increased to 21.4% in those with more than one comorbidity. Other risk factors for mortality were fungal infections, sepsis and pneumonia. Mortality is obviously a severe concern, but hospitalisation and prolonged illness also carry major healthcare costs.

Myelosuppressive chemotherapy-induced neutropenia causes a range of problems, including febrile neutropenia and increased risk of severe infection. It also leads to delays in chemotherapy doses and dose reductions. The dose may be reduced either by giving a smaller amount of drug, or by extending the time over which it is given, resulting in a reduction in dose intensity. Both can lead to reduced survival.

There are reasonably good data to indicate that dose intensity is very important. The strongest data come from studies in early-stage breast cancer. A retrospective study carried out by Bonadonna et al, following up patients for at least 20 years, showed that relapse-free survival and overall survival decreased in line with chemotherapy dose intensity (*NEJM* 1995, 332:901–906). Survival in a study by Pfreundschuh and colleagues of patients with non-Hodgkin's lymphoma (another chemotherapy-sensitive cancer) showed similar results (*Blood* 2004, 104:634–641). There may be some cancers where chemotherapy is less

CUMULATIVE RISK FACTORS



Five significant risk factors for febrile neutropenia have been identified – the more risk factors a patient has, the higher their risk of febrile neutropenia

RDI relative dose intensity, ANC absolute neutrophil count
Source: Personal communication, Lyman et al, ANC study group, Duke University, USA

MULTIVARIATE ANALYSIS OF RISK

Covariate	Adjusted odds ratio* (95% CI) All patients 6 cycles (n = 4,522)
Age > 60 years	2.28 (1.96-2.67)
Stage >III	1.18 (1.01–1.39)
ECOG performance status >2	1.28 (1.01–1.64)
Albumin <3.5 g/dL	1.26 (0.98–1.62)
Prophylactic G-CSF	0.70 (0.55–0.89)

An analysis of risk factors in patients whose treatment was reduced to less than 85% of recommended dose intensity showed that being aged over 60 was the biggest single risk factor

*Adjusted for year of treatment, planned duration of treatment and practice site

Source: GL Lyman et al. Incidence and predictors of low chemotherapy dose-intensity in aggressive non-Hodgkins's lymphoma: A nationwide study. *JCO* 2004; 22:4302-4311

effective, but overall it is clear that giving full-dose, or standard-dose, chemotherapy is the way to achieve the best outcome for patients.

It is very important to be aware that relative dose intensity (a measure of the delivered dose intensity as a proportion of the standard dose intensity) is often underreported in randomised controlled trials and long-term outcomes are also not reported. However, when data are available, we have found that dose reductions are very common. The strongest data suggest that a reduction in the dose to less than 85% of what would be predicted to be optimal therapy is quite common in many cancers (Dale et al, *JNCCN* 2003; 1:440-454).

A study of breast cancer adjuvant chemotherapy for a large US population showed that around 50% of patients received less than full-dose chemotherapy. This is a concern, and we should aim to optimise therapy by finding ways to give treatment at the dose that has been shown to be effective in randomised trials.

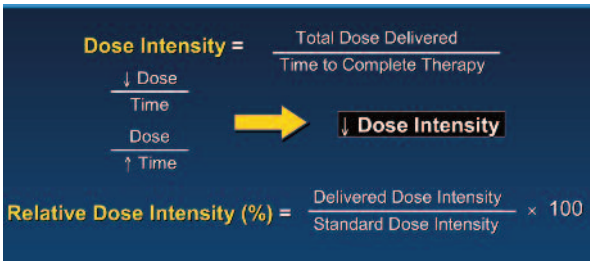
Management strategies

To reduce the risk of neutropenic events, including infections, and to avoid dose reductions in the course of giving cancer chemotherapy, our focus has been on prevention. Treatment of patients with febrile neutropenia admitted to hospital has improved modestly over the years, with better supportive care and better antibiotics, but problems remain, and prevention is the most important strategy to reduce the risk of undertreating or infections in the course of giving cancer chemotherapy.

There are three approaches:

- delay or reduce the drugs
- administer prophylactic antibiotics
- give haematopoietic growth factors or myeloid growth factors in a prophylactic strategy.

DOSE REDUCTIONS



Dose reduction

There is little or no evidence that using a dose below 85% of that recommended is favourable for any patient group, although it is a common strategy in palliative care to try to maintain a patient's quality of life and days that they have to live.

Prophylactic antibiotics

A large randomised trial conducted by Cullen et al., comparing the quinolone antibiotic levofloxacin with placebo in preventing infection associated with cancer chemotherapy in a large and diverse group of patients, mostly with solid tumours, showed that the antibiotic reduced the occurrence of febrile neutropenia. However, it did not reduce deaths (*NEJM* 2005, 353:988-998).

There are several issues associated with this approach, including that the risk of giving prophylactic antibiotics to the large numbers of patients undergoing treatment with cancer chemotherapy may result in the development of resistant organisms that might cause infections later in cancer treatment.

A second international study with levofloxacin in patients with cancer and neutropenia, carried out by Bucaneve and co-workers, also showed that it was effective in reducing febrile episodes (relative risk 76%), but there was no significant effect on infectious deaths or overall deaths (*NEJM* 2005, 353:977–987). The results show the benefits of antibiotics in reducing the number of bacteria in the short term. However, based on clinical experience, this is only a short-term effect, because the body surface is a rich place for bacteria and fungi to grow, and suppressing some organisms enables others to rapidly emerge.

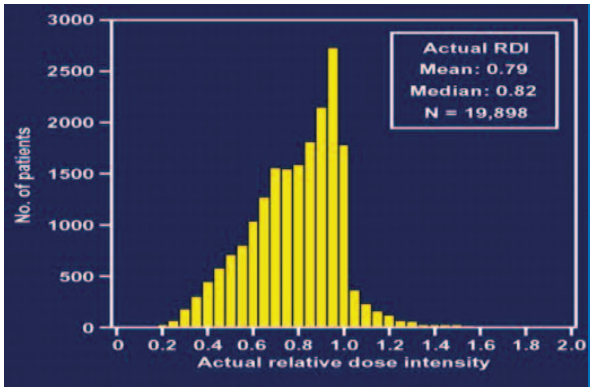
Haematopoietic growth factors

Haematopoietic growth factors have been a research interest of mine for a long time, both at basic and clinical levels. Colony stimulating factors, or

myeloid growth factors, were discovered in the 1960s, utilising a simple Petri dish culture system. Discovering how to grow blood cells *in vitro* was a dramatic event – very important in the history of haematology and in the development of modern medical oncology.

Probably the most important finding in this research was the discovery of the specific factors that regulate haematopoiesis. Out of this work came the drug we call G-CSF – granulocyte colony stimulating factor – which is a relatively small glycoprotein produced in many cell types in the body, in response to a range of stimuli including injury or infection. Over time, it was learned that the levels of G-CSF in the body regulate the production of neutrophils.

REDUCED DOSE INTENSITY IS COMMON



The number of breast cancer patients found to be on a reduced dose intensity is a cause for concern, given what is known about the impact of reductions in dose intensity on survival

Source: GL Lyman et al. Incidence and predictors of low dose-intensity in adjuvant breast cancer chemotherapy: A nationwide study of community practices. *JCO* 2003; 21:4523–4531. Reprinted with permission. © 2008 ASCO. All rights reserved.

We now know that levels of G-CSF increase abruptly when a patient develops an infection. However, becoming gradually neutropenic – as occurs with cancer chemotherapy – does not usually cause G-CSF levels to rise until neutrophils have reached a very low level. The problem with the onset of neutropenia after cancer chemotherapy is that the signal to recover neutrophils occurs late, and gradual recovery occurs if you wait for this natural response.

This understanding led to the development of an important clinical use of G-CSF as a drug to accelerate neutrophil recovery after chemotherapy. G-CSF has often been compared to GM-CSF – granulocyte-macrophage colony stimulating factor – because it had similar effects in the early studies in the Petri dish model. However, GM-CSF is a distinctly different molecule and is produced by different cells, particularly T-cells and monocytes. Experimental studies have shown that deficiencies of G-CSF cause neutropenia, but deficiencies of GM-CSF do not. GM-CSF is a very different agent biologically, with different clinical effects.

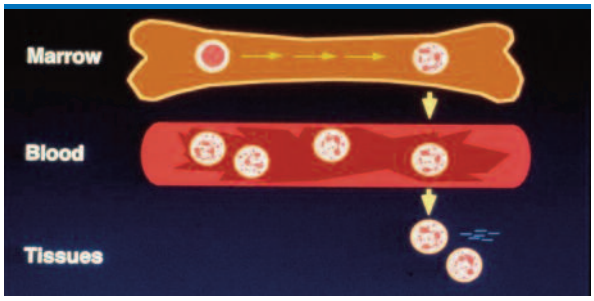
G-CSF/FILGRASTIM

G-CSF, or filgrastim (a G-CSF analogue), has a helical structure, which gives the molecule its three-dimensional shape, which is key for interacting with its receptor on myeloid cells. G-CSF acts specifically on myeloid cells that have a receptor for the molecule. G-CSF stimulates neutrophil proliferation and accelerates the delivery of neutrophils from the bone marrow into the blood. Normal neutrophil development and deployment occurs at three levels. In the marrow, cells develop from stem cells to mature neutrophils. In the blood, neutrophils flow along with the red cells, but they stick at sites of inflammation. In the tissues, they migrate to fulfil their function in the containment and killing of bacteria and in mounting a response to infection.

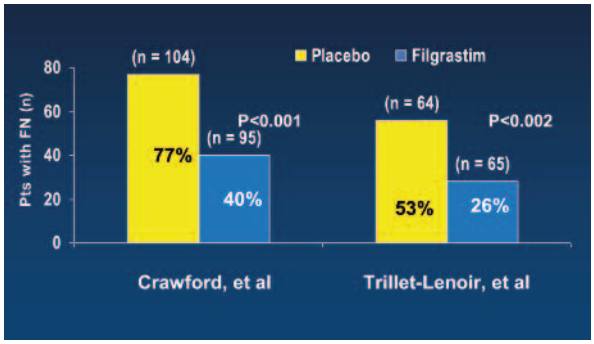
In studies to understand the role of G-CSF, we gave these agents to healthy young and elderly volunteers. We were interested in the ageing process and whether older people would respond less well. The studies showed that age does not block the response to G-CSF. The bottom line is that a wide range of patients with different comorbidities and varying in many other factors, including age, all respond to G-CSF quite well, if they have haematopoietic cells in their marrow that are capable of responding.

An important point in terms of oncology practice is the effect of G-CSF and GM-CSF on marrow transit time. In our studies we looked at how these agents stimulate the flow of cells through the bone marrow. With no drug, the time for production of a neutrophil, from the last stage of dividing cells to a mature neutrophil in the marrow and its entry

NORMAL NEUTROPHIL KINETICS



BENEFIT OF G-CSF/FILGRASTIM



G-CSF/filgrastim has been shown to result in a significant reduction in cases of febrile neutropenia among cancer patients receiving chemotherapy

Source: Adapted from J Crawford et al. *NEJM* 1991; 325:164–170; V Trillet-Lenoir et al. *Eur J Cancer* 1993; 29A:319-324

into the blood, was about six days. Giving G-CSF accelerates the time for maturation of neutrophils and their entry into the blood. We showed that G-CSF can reduce the time for maturation and deployment of neutrophils by about 50%, reducing the time for cells to transit through the marrow to the blood from approximately six to three days. By stimulating neutrophil production and entry into the blood, G-CSF helps to increase the accumulation of these cells at sites of infection and inflammation.

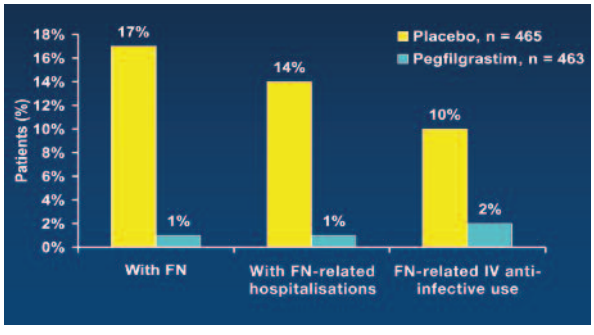
Crawford and Trillet-Lenoir and their co-workers were early investigators of G-CSF in cancer chemotherapy; their work emphasises the principles mentioned above. Their reports were the first to demonstrate a reduction in the occurrence of febrile neutropenia in randomised controlled trials (*NEJM* 1991, 325: 164-170; *EJC* 1993, 29A:319-324). Their studies showed that G-CSF accelerates neutrophil recovery after chemotherapy; the return of blood neutrophils was much faster in the G-CSF treated patients.

In subsequent clinical trials, Timmer-Bonte and others demonstrated the same effects of G-CSF use to prevent febrile neutropenia with less myelotoxic chemotherapy regimens. For example, in the trial by Crawford et al, there was approximately a 60% risk of febrile neutropenia. In the Timmer-Bonte trial, patients had approximately a 30% risk of febrile neutropenia, and G-CSF treatment also reduced this risk by about 50% (*Proc ASCO* 2004, 23:726).

This is such an important development that there have been many efforts to improve on it over the years. The most valuable was the development of the pegylated molecule (pegfilgrastim), adding polyethylene glycol, making the G-CSF molecule bigger and thereby reducing its renal clearance.

A clinical trial carried out by Vogel and co-workers showed that using pegfilgrastim in patients who were treated with less intensive chemotherapy and whose risk of febrile neutropenia was only approximately 20% virtually eliminated the risk of febrile neutropenia (*JCO* 2005, 23:1178-1184).

BENEFIT OF CSF/PEGFILGRASTIM



Pegfilgrastim virtually eliminated febrile neutropenia in cancer patients at 20% risk of developing the condition

Source: Vogel et al. First and subsequent cycle use of pegfilgrastim prevents febrile neutropenia in patients with breast cancer: A multicenter, double-blind, placebo-controlled phase III study. *JCO* 2005; 23:1178–1184

Issues in the use of G-CSF

Although these data are very sound and we can rely on them to set the guidelines in cancer practice, many questions remain. These include whether the dose of G-CSF can be reduced, whether there is a difference between G-CSF and pegylated G-CSF, the place of GM-CSF versus G-CSF, and the use of G-CSF with other drugs such as corticosteroids, which also raise neutrophil counts. There are also questions about timing – should we give G-CSF early, late, or for a few days? Many of these questions have general answers, although most have not been subjected to large randomised trials.

Because the myeloid growth factors G-CSF and GM-CSF can stimulate proliferation of both the normal and leukaemic cells, researchers and physicians have been concerned about the potential risks associated with their use. Recently the ANC study group performed a meta-analysis to investigate the risk of myelodysplasia and leukaemia associated with the use of G-CSF as part of supportive care for patients

receiving cancer chemotherapy. A systematic review of randomised trials compared the outcomes for cancer patients receiving either chemotherapy alone or chemotherapy plus G-CSF. The study showed a small but statistically significant increase in the occurrence of leukaemia in patients who were randomised to receive G-CSF. On the other hand, overall mortality rates were lower in the patients treated with G-CSF. The G-CSF treated patients also receive more chemotherapy – a finding that complicates the interpretation of these data, because many commonly used myelotoxic drugs can cause leukaemia. There are also other limitations that make these data and similar studies difficult to interpret. The trials were obviously not conducted to see whether treatment causes leukaemia; it is only observed as an adverse effect. There were also variations between trials in the way adverse effects were described and how long the patients were followed before the results of the trial were reported. Some of the 'control' patients may also have been given G-CSF, if they seemed to need it. This study was presented and discussed at the American Society of Hematology meeting in December 2009.

Nevertheless, the increase in leukaemia with G-CSF treatment was about 0.4% and supportive care with G-CSF is associated with an absolute reduction in all-cause mortality of about 3%–4%.

ASCO guidelines on the use of white blood cell growth factors recommend that G-CSF should be used when there is a risk of febrile neutropenia of greater than 20%, unless the treatment is symptomatic or palliative, when dose reduction is usually appropriate. The guidelines also say that primary prophylaxis – the use of CSFs for prevention in the first cycle of treatment – should always be considered for older patients, or where the patient's medical history or other disease characteristics suggest that there is substantial risk of febrile neutropenia.

The National Comprehensive Cancer Network (NCCN) CSF guidelines recommend focusing on three aspects of each patient when determining risk for febrile neutropenia:

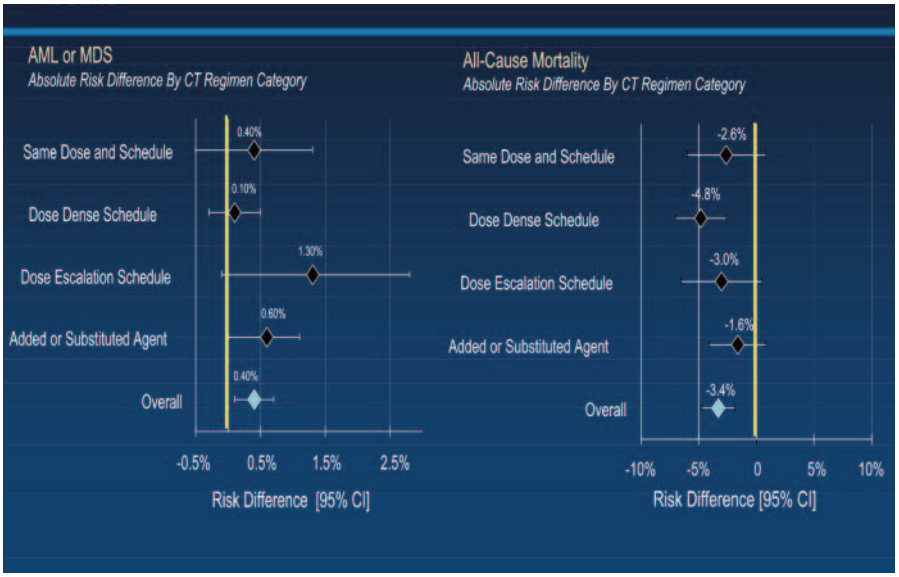
- Patient-related aspects: age, gender, performance and nutritional status, comorbidities,
- Treatment-related aspects: neutropenia, drugs – anthracyclines, relative dose intensity,
- Cancer-related aspects: some cancers, including haematological malignancies and lung cancer, and all cancers at advanced stage, predispose patients to infections.

The NCCN growth factor algorithm for prophylaxis with growth factors addresses whether chemotherapy is curative, intended to prolong survival or to help with symptom management, or palliative. For cases with a >20% risk of febrile neutropenia with chemotherapy, the CSFs have a benefit that should be considered. CSFs should not be used where the estimated risk is less. In summary:

- Use G-CSF if there is a high risk of febrile neutropenia (>20%) with curative intent, to prolong survival, to improve quality of life.
- Consider G-CSF if risk of febrile neutropenia is 10%–20%.
- Do not use G-CSF if risk of febrile neutropenia is <10%.

Each patient should be assessed for their risk of febrile neutropenia, and decisions on whether to give CSFs should be based on this risk.

BENEFITS OUTWEIGH RISKS



A review of randomised controlled trials showed a small but significant rise in leukaemia among cancer patients receiving G-CSF as supportive care, but this was far outweighed by the fall in mortality

Source: American Society of Hematology Meeting, December 2009

Jeffrey Crawford (JC), of the Duke University Medical Center, in Durham, North Carolina, USA, explored some of the issues further with David Dale (DD).

JC: *Can we generalise that the standard dose of chemotherapy is standard for all patients, or do we need to think about differences in patients in terms of tolerance to chemotherapy?*
DD: It is important to see the differences between patients and patient groups. Age is a critical differentiating factor: it bundles together comorbidities and many other factors. Patients over the age of 65, or certainly over age 70, should always be considered at risk and therefore potential candidates for some prophylactic strategy.
A second differentiating factor is the patient's blood cell counts. Patients who have evidence of previous haemotoxicity from drugs or disease are at greater risk, particularly if they have a low white cell count or low neutrophil count. The general physical examination and basis blood count also help us to easily identify patients at greater risk of febrile neutropenia and other complications.
Another differentiating factor is the specific drug to be given in the planned chemotherapy regimen. This is a complicated area, because there are so many drugs and combinations. The NCCN guidelines (readily available at nccn.org) provide the best information available about relative risk of neutropenia and severe neutropenia with different drugs.
JC: *Should there be differences in dosing based on different ethnic populations?*
DD: There are probably ethnic differences, but we do not know very much about them. For example, the African/American population tends to have somewhat lower baseline white blood cell and neutrophil counts than other groups, but seems to tolerate chemotherapy equally well.
JC: *How should one calculate the dose of chemotherapy for an obese patient?*
DD: This is another confusing area. We generally use the body surface area or ideal body weight instead of body mass, as the index for dosing, but there is a point at which there is considerable uncertainty.
JC: Larger patients tend to be underdosed if you use the ideal body weight rather than the actual body weight when delivering standard chemotherapy doses. Even though they are getting larger total doses, the body surface area corrects for most of that. One of the concerns about the poor outcomes for obese women with adjuvant breast cancer may be that they are relatively underdosed. Some data suggest that they have less neutropenia, so you should at least use the standard of total body weight and surface area in your calculations.
There is also literature around about the importance of neutropenia as a surrogate endpoint for chemotherapy effectiveness. There are data on lymphoma and other settings that patients who develop some degree of neutropenia have a better outcome than those who do not. The same has been shown in advanced-stage lung cancer. This gets back to the question, if we could individualise therapy, what would be the right dose? Presumably what is happening is that there is enough pharmacogenomic variation in how individuals handle drugs that one dose probably does not fit all. But knowing the dose that achieves cytotoxic effect on the patient and that treats their tumour requires further study.
JC: *Can you comment on the functional effects of G-CSF and GM-CSF? You spoke about neutrophil numbers, but what are the functional effects when these cytokines are active in our bodies?*
DD: This is a very interesting area. G-CSF has many effects beyond stimulating neutrophil production. It also activates many processes in the cell. For example, it stimulates the formation of the enzymes that go into the granules of neutrophils, particularly the primary granules that are involved with the killing of organisms. G-CSF also 'primes' neutrophils, so that they have a greater metabolic burst and greater oxygen and glucose consumption when they are exposed to bacteria or other foreign particles. All of these changes can be seen as part of the host response to infection to enhance the body's capacity to deal with an infection.

Conclusions

Neutropenia, febrile neutropenia and reductions in chemotherapy dosing remain serious problems in medical oncology. Delivering chemotherapy at standard doses and on schedule is important in optimising outcomes. There is good physiological and clinical evidence for the use of G-CSF to prevent febrile neutropenia and ameliorate the myelotoxicities of cancer chemotherapy. Evidence-based medicine and clinical guidelines support the use of G-CSF to prevent chemotherapy-induced neutropenia. Prophylactic antibiotics are alternatives to the CSFs. Treatment of febrile neutropenia, when it occurs, requires very careful attention to the patient, prompt antibiotic therapy and good hospital care.

MRI for breast cancer: who benefits, who is harmed?

Emma Mason

When a woman is diagnosed with breast cancer, and a technique exists that could identify additional lesions in the same or the opposite breast, what possible reason could there be for not using it? Unnecessary delays and unnecessary mastectomies to name but two, say the opponents of routine MRI. The debate continues.

At the European Breast Cancer Conference in Barcelona this year, one of the closing debates is entitled: "This house believes that MRI for breast cancer is standard of care" – thus tapping into a controversy that has been the subject of much research and discussion in recent months and years.

For many it is not at all clear that magnetic resonance imaging (MRI) should be used routinely in the diagnosing, staging and treatment of breast cancer. In fact, a number of influential voices have been asking whether MRI does more harm than good, particularly before surgery in women with uncomplicated early breast cancer.

Speaking against the motion at EBCC7 in Barcelona will be Lawrence Solin, chairman of the Department of Radiation Oncology at the Albert Einstein Medical Center, in Philadelphia, USA. In a recent article for *The Breast* (in press) Solin argues that a medical test or treatment should be of benefit to patients if it is to be used in routine clinical practice, and that, for the typical patient with early-stage breast cancer, "no such benefit has been shown to date for the routine use of preoperative breast MRI beyond the benefit already conferred by conventional breast imaging (i.e. mammography with correlation ultrasound as indicated)." Thus, he concludes, the routine use of preoperative breast MRI for early-stage breast cancer patients is unwarranted.

Others go further, pointing to a potential link between increased use of MRI and a rise in the rate of mastectomies, many of which may be unnecessary. In an editorial for the *Journal of Clinical Oncology* last September, Monica Morrow, head of the Breast Surgery Service at New York's Memorial Sloan-Kettering Cancer Center, argues that the assumption that using MRI to select patients for breast-conserving therapy would reduce the need for re-excision, reduce local recurrence, and even improve long-term survival does not seem to have been borne out in practice. "At present, no studies have provided support for any of these improved clinical outcomes," she writes. "However, breast MRI has been shown to result in additional biopsies and costs, increased patient anxiety, and delays in the start of definitive treatment." She points out that while accepted practice is for MRI-detected abnormalities to be biopsied before altering surgical treatment plans, some patients choose to forgo these biopsies or additional work-ups and opt to go straight for mastectomy, "because of concerns about delaying definitive therapy."

GETTY IMAGES

"The detection capability of this technique is such that it would be wrong to wait for conclusive evidence"

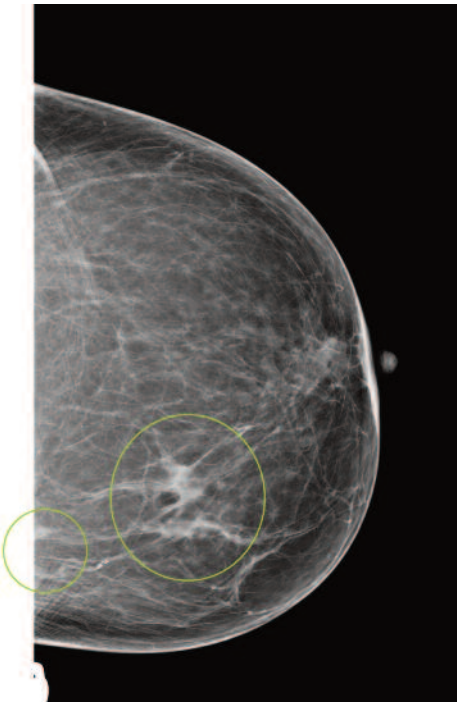
A VERY GOOD TECHNIQUE

At the heart of this debate is the undisputed fact that MRI is an extremely good imaging technique. It can detect tumours that are missed by more conventional techniques such as mammography and ultrasound, it is better at correctly assessing tumour size and detecting additional foci of disease (multi-focal or multi-centric cancers, or both), and it is better at detecting abnormalities in the dense breasts typically seen in younger women.

Francesco Sardanelli, professor of radiology at the University of Milan School of Medicine and head of the Radiology Unit at the IRCCS Policlinico San Donato in Milan, Italy, pioneered the use of MRI in breast cancer in Europe. Writing in *The Breast* (in press), he argues that the detection capability of this imaging technique is such that it would be wrong to wait for conclusive evidence for or against preoperative MRI. "To deny this examination to all women newly diagnosed with breast cancer is a questionable decision because the evidence is 'uncertain' rather than against a benefit from preoperative MRI."

Morrow disagrees. "It seems very obvious that something that shows the cancer clearly must be a good thing for patients," she told *Cancer World*, "but there is an increasing body of data that shows that, so far, this doesn't seem to be true."

Indeed, the success with which MRI picks up even the most minor abnormalities is exactly where the problem lies, she says, as many of these will be false-positives – benign abnormalities or cancers so tiny that they would be dealt with effectively by radiotherapy during or after surgery, or by systemic therapies such as endocrine or chemotherapy.



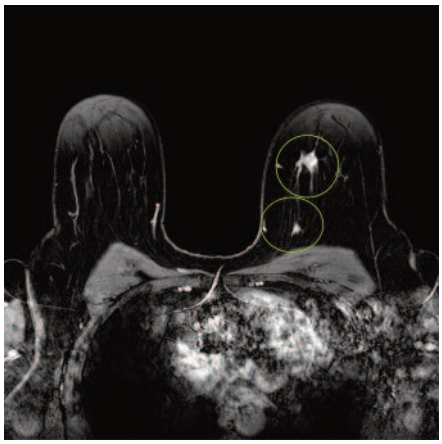
This multifocal lobular breast cancer was picked up using normal mammography (upper), but MRI was instrumental in clarifying the real extent of the disease (lower)
By permission of Elena Cauzza

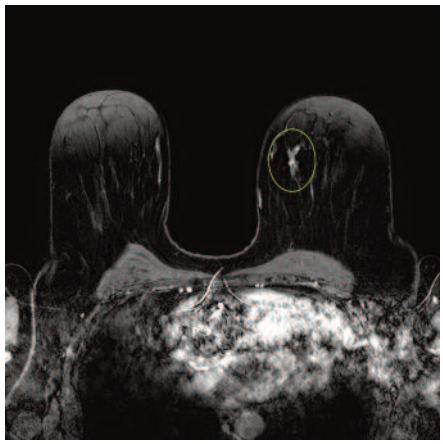
"There's fairly convincing evidence that says that MRI shows a lot of small-volume disease that's always been there and that's successfully treated with radiotherapy, but when we see it we feel obliged to do something about it, and that something is usually mastectomy," she said.

"So far what we know about MRI is that it doesn't increase your likelihood of getting negative margins with a single lumpectomy. It does not decrease the risk of unexpected conversion from lumpectomy to mastectomy, and although the data with longer-term follow-up are still very limited, what there are show that it doesn't decrease the risk of local recurrence in the breast.

"So, of any of the potential benefits to patients, none of them have been proven. What we do know is that it can delay treatment, it results in more biopsies, and it increases cost."

In a review of preoperative MRI, published in *CA: A Cancer Journal for*





"When we see it we feel obliged to do something about it, and that something is usually mastectomy"

Clinicians last September, Nehmat Houssami and Daniel Hayes make a similar case. "Evidence consistently shows that MRI *changes* surgical management, usually from breast conservation to more radical surgery; however, there is no evidence that it *improves* surgical care or prognosis." Like Morrow, they argue that the emerging data indicate that MRI does not reduce re-excision rates and that it causes false-positives in terms of detection and unnecessary surgery.

The authors also point out that, while local recurrence rates are between 5% and 10% for breast conserving surgery combined with radiotherapy, a meta-analysis has found that MRI detected additional small cancers in the same breast in 16% of cases on average. "That's more than twice as many as the number of woman who ever develop evidence of a recurrence," says Morrow, commenting on these findings, "and I think this is evidence that this type of disease does not need to be treated surgically."

From the patient's point of view, MRI gives more information, but can increase the complexities of the decision-making process, for both her and her physician.

If an MRI shows up suspicious tissue elsewhere in the affected breast, or the contralateral breast, then international guidelines recommend that an MRI-

CLAIMS AND COUNTERCLAIMS

Supporters of routine use of MRI argue that it offers a number of benefits:

- by visualising the size and extent of the disease, it can enable surgeons to excise the correct amount of tissue, removing the tumour entirely, while not removing unnecessarily large quantities of healthy tissue;
- this, in turn, reduces the likelihood of re-excision to remove remaining tissue that turns out to be cancerous;
- it can reduce rates of the tumour recurring in the same breast;
- it detects other tumours in the same breast (ipsilateral cancer) or the other breast (contralateral cancer), enabling surgeons, in theory, to remove all tumours in one go;
- it can visualise whether preoperative treatment, such as radio-, chemo- or hormonal therapy, is having an effect in shrinking a tumour before surgery, possibly enabling a lumpectomy to be performed rather than a mastectomy;
- it can visualise whether the same treatments are mopping up small cancerous deposits after surgery;
- it provides better images of dense breasts;
- it is better at detecting certain cancers, such as invasive lobular breast – a particularly aggressive cancer;
- all of the above could lead to an improvement in recurrence and overall survival rates.

Opponents counter that, while many of the benefits listed above were expected when MRI was first introduced for breast cancer, they have not been borne out in reality.
They argue that, on the basis of the evidence so far, MRI:

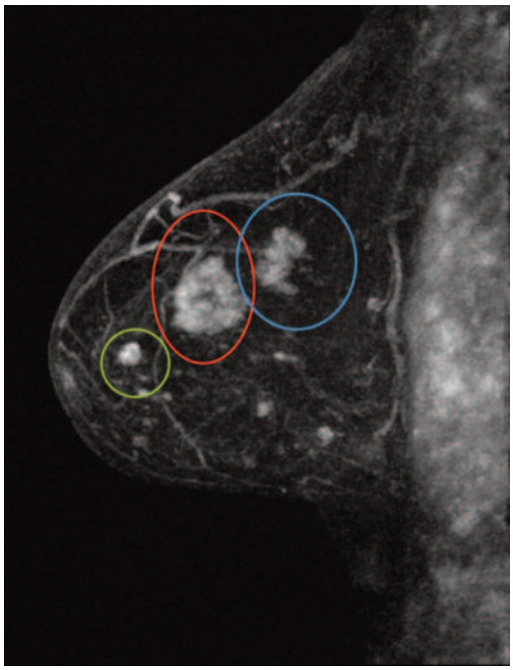
- does not increase your likelihood of getting negative margins with a single lumpectomy;
- does not decrease the risk of unexpected conversion from lumpectomy to mastectomy ;
- does not decrease the risk of local recurrence in the breast.

It does, however, lead to:

- additional biopsies and costs;
- increased patient anxiety, and
- delays in the start of definitive treatment.

"MRI *changes* surgical management, however, there is no evidence that it *improves* surgical care or prognosis"

"Some people want to diagnose every little patch and are not aware of what really threatens the patient's life"



MRI scans have a high false-positive rate. On this scan, the area circled in blue showed a highly significant signal, yet nothing was found on pathological investigation. The area circled in red was found to be an invasive cancer, and the area in green a fibroadenoma

By permission of Elena Cauzza

guided biopsy should investigate the tissue. This delays the diagnosis and the start of treatment, and introduces yet another procedure to undergo. Already anxious and stressed by the initial diagnosis of breast cancer, many women decide that they can't face the added delay and uncertainty involved in having a biopsy, and opt to go straight to a mastectomy in the hope that this will deal with all the cancer in one go.

Other factors may also play a role in the decision to opt for mastectomy, such as the availability of MRI-guided biopsies, how they are funded (does it require extra permission from the health insurers, hence further delay), cultural differences, the medical-legal climate of a country and the availability of plastic surgery.

Loss of focus

The radiologist, physician and patient also have to focus on what is the main threat to the patient's life. Sylvia Heywang-Köbrunner, director of the Referenzzentrum Mammographie München, a mammography reference centre in Munich, Germany, told *Cancer World*, "In my experience, when you do an MRI and find something that is enhanced, that does delay surgery. We all try very hard to schedule the biopsy quickly, but this can be difficult and you may also need to consider the woman's menstrual cycle, so that you pick the right time of the month."

Delaying treatment of a large, grade III tumour on the grounds that MRI has indicated there may be an additional small lesion could make things worse, she argues. "For me, the big question is: do I help the patient by finding a small, 3- to 5-mm lesion elsewhere in the breast or in the contralateral side, if the patient's life is really threatened by the first, large tumour?

"Sometimes people want to diagnose every little patch and are not aware of what really threatens the patient's life. One should really consider which patients can we help with MRI and which patients might we delay the diagnosis and cause more problems than we solve.

"I think we should be very careful not to over-read and overtreat. We still need to prove whether, by finding additional tiny foci, that's helpful for the patient, because we cause harm by converting from breast reconstruction to mastectomy if the patient has no better survival."

Who needs MRI?

So when should MRIs be performed and when not? Most commentators seem to agree about when they can be useful, but there is less agreement about when MRI should be avoided, with some proponents of the technique arguing that it should always be used because of the extra information it provides.

Morrow and Heywang-Köbrunner both argue against using MRI in uncomplicated early breast cancer where other imaging techniques suffice.

"I definitely would not recommend MRI in breasts that are adequately analysed by mammography and ultrasound, or by a combination," says Heywang-Köbrunner. "This combination has an acceptable sensitivity [proportion of true-positives correctly identified], especially for the lesions that are larger than 5 mm; the false-positive rate is much lower than MRI and, importantly, it's very easy to clarify something that I see. For instance, if I see something on mammography or ultrasound, a mammographically-guided procedure or ultrasound-guided procedure can be done very fast, it's reliable and you have the people available who can do it and this is solved very easily."

She does, however, recommend an MRI in dense breasts and where lobular

When MRI throws up false-positives

MRI tends to throw up more false-positives than either mammography or ultrasound, and great care must be taken when using preoperative MRI to guide decisions on surgery.

The most frequent causes of false-positives include adenosis (a benign condition affecting the lobes in the breast) and benign tumours such as fibroadenomas or papillomas. Less frequently, inflammatory changes, granulomas or lipo-filling may cause confusion.

Lipo-filling is a new technique in plastic surgery which involves aspirating fat tissue from another part of the patient's body and then re-injecting it into the areas of the breast that are not completely filled, making it possible to shape the breast better. But breast surgeon Alberto Costa warns that on MRI it can be mistaken for an area of cellular growth. "This happened to me, when the radiologist saw this and rang me to say that here were multiple recurrences and we needed to do an immediate mastectomy," says Costa. "Luckily we worked out what the problem was."

Even when the MRI shows real cellular growth, he adds, while it may be cancer, it may also be general growth, such as a scar. "So if you do magnetic resonance too soon after surgery, it's biased because it will flag up areas of cellular growth that are simply the process of scarring after surgery. So you never do MRI after surgery earlier than at least a month or six weeks."

breast cancer has been diagnosed, "because we know that mammography and ultrasound is weak in these situations and might not detect quite large tumours that could threaten the patient's life, or would make a change of therapy necessary."

MRI may also be beneficial, she adds, in women who are at high risk of inherited breast cancer, in young women with dense breasts, in cases where there is a big discrepancy in the size of the tumour when measured by mammography and ultrasound and possibly also to help a surgeon who is uncertain about whether mastectomy or breast reconstruction is the best way forward.

Heywang-Köbrunner would like to see research to find out whether MRI can offer early evidence if a certain treatment, such as chemotherapy, is not working. "If we can find this out early on, we can suggest a change of chemotherapy so that the patient does not lose time on a treatment that is not going to work."

The right questions

Morrow agrees that more research is needed to establish where the information provided by MRI might help. "For example, one such clinical problem is women who received chemotherapy prior to surgery to shrink their cancers to allow a lumpectomy; it's very difficult to evaluate how much cancer is actually present. And that's a place where MRI appears to be better than other tools that we have."

What we don't need, she says, is yet another general study of MRI for all breast cancer patients, "because I think that question 'can it find more cancer?' has been asked and we know the answer is yes, but that doesn't say that it benefits patients." Questions about whether MRI can identify a subset of patients who don't benefit from radiotherapy or a subset who are appropriate for radiating only part of the breast, would, however, be useful to investigate, says Morrow. "There's room for more of these trials that ask about the benefit to patients."

One thing that most people agree on is the need for expertise in the use and interpretation of MRI. Alberto Costa, director of ESO (the European School of Oncology), and coordinator of both the Breast Surgery Unit at the Maugeri Foundation in Pavia, Italy, and the Canton Ticino Breast Unit in Lugano, Switzerland, summed it up: "You need to have a radiologist who is specialised in magnetic resonance imaging and then sub-specialised in breast cancer. Otherwise, MRI can create incredible disasters. It's a very good technique, a new technology, which could be of great help in genetically predisposed women, in preoperative medical treatment and in a number of other situations, but which, in not very expert hands, could create damage because it can overestimate the diagnosis."

More research is needed to establish where the information provided by MRI might help

From unwanted interference to indispensable partner

The patient advocate who helped open the minds of Europe's cancer doctors

➜ Simon Crompton

As founding president of Europa Donna, the European Breast Cancer Coalition, **Gloria Freilich** helped transform attitudes towards patient advocacy. She would like to see further progress, particularly in regions that have been slow to accept a patient role, and advises that her softly softly approach – building confidence and allaying suspicions – is the way to go.

Three years after taking up the presidency of Europe's first international breast cancer coalition, Gloria Freilich faced her most embarrassing moment. It was 1997 and she had started to address a major meeting of oncologists in Lisbon, talking about her new organisation, designed by women for women, called Europa Donna. Then a doctor stood up and challenged her. What right did a layperson, he asked, have to address a thousand oncologists at a medical meeting?

Freilich was flabbergasted. Many of the doctors there were too. She gathered herself, and answered that she had a right to be there because she was representing the other side of the medical equation – the patient viewpoint. Then she carried on with her presentation, uninterrupted.

Recalling the event 13 years later, her presidency of Europa Donna now in the past, it still makes Freilich's toes curl. Nowadays, such an incident would be unthinkable. It's a mark of how much Europa Donna has helped change attitudes that the patient viewpoint is now intrinsic to top-level international discussions about breast cancer. Under Freilich's leadership, a European breast cancer organisation representing the interests of patients earned a place at the scientific table not by confrontation, but by instilling respect among medical colleagues. The process hasn't always been easy.

So Freilich's proudest moment came three years later when, after the end of her presidency, she stood up again to speak, this time in Strasbourg to 90 Members of the European Parliament and the then European Health Commissioner David Byrne. When Europa Donna had been set up, its instigator, surgeon Umberto Veronesi, told Freilich that its aspiration should be to address the European Parliament and gain its support for improving diagnostic and treatment services across the whole continent.

Now, by a strategy of making the patient voice indispensable rather than an unwanted interference, it had achieved this aim. In her Strasbourg address, Freilich emphasised the need for a European breast

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cancer registry, rapid access to treatment, multidisciplinary breast units and equalisation of services throughout Europe. This prepared the ground for major developments that have followed, such as the European guidelines for quality assurance in breast cancer screening and diagnosis – now a fundamental tool that Europa Donna coalition members use to advocate for better services in their countries.

Appropriately enough, Freilich's role in this transformation started from her own distressing experiences of cancer. It all began with an error. In 1983, living in London, she decided she should have a general health check-up and mammogram. Her mother had died of breast cancer 10 years earlier, and her cousin and aunt had also died of the disease shortly after diagnosis. So there was good reason for having a check, even though there was as yet no national screening programme in the UK. When she arrived at the hospital, the mammogram machine had broken down. So she had to go to another, where the machinery had a peculiar balloon contraption instead of a plate to hold the breast in place.

"I must say, I remember it very well because it was very difficult not to laugh while it was happening," says Freilich. "You were kind of squashed down under this balloon, and it was only a single view of each breast, not two views as one would expect now. And I was told that everything was fine."

"That summer I went away on holiday with my husband to Italy. It was two months after I'd had the mammogram, and pulling my swimsuit up I found a lump about the size of a plum in my left breast. I said nothing at the time, but when we got back to London I rang the breast surgeon's secretary and made another appointment. When I went in, I had a needle put into the lump. Shortly afterwards, I was telephoned at my office – I was working as the fundraising officer for the National Autistic Society at the time – and I was told there and then, on the telephone, that it was cancer."

It was a terrible blow. It felt like a family destiny that she should die of cancer too. Freilich remembers being in such a state that she accidentally set fire to her dressing gown – thankfully she was unhurt. Her husband and her twin son and daughter, who were 15 years old and studying for their 'O' level exams, were "desolate". So she returned to hospital and had a segmental mastectomy and complete axillary node clearance. Histology came back with its analysis. It was not cancer.

At the time, Freilich was overjoyed at the news, but nowadays, she reflects, patients might sue under

Cancerkin, Hyde Park, 2005. Every other year, patients, families, friends, health professionals and celebrity supporters gather in London's most famous park for a 10km walk to raise funds for the breast cancer advocacy group

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similar circumstances. She had to perform an enormous psychological turnaround and was left with conflicting emotions – a knowledge of how gruelling a diagnosis of cancer was, an awareness of the inadequacies of some services, but also a deep gratitude at being spared.

Getting involved

To this point, almost every experience she had had of cancer had been negative. The one thing that had impressed her was the care given to her at the Royal Free Hospital (the misdiagnosis had been a laboratory error). She stayed in touch with her surgeon, Santilal Parbhoo, and offered to help with a breast cancer research appeal he was setting up. Freilich set about raising money, not only for clinical research but for a new clinic for women at high risk of breast cancer, and a new computerised call and recall system. On the basis of her success with this, she was invited to help set up and run new patient services, as a full-time, professional job.

With a background in music – she had studied to be a pianist and opera singer before starting a family – she was aware of gaps in her scientific knowledge and attended lectures for medical students. "I was allowed to build up my knowledge and confidence," she says. "So I started to suggest, there's little here to inform or support patients. Couldn't we do something about that? I took a counselling course and prepared to set up this organisation for patients, which in 1987 became Cancerkin."

Cancerkin, which Freilich led as chief executive

Freilich was overjoyed, but nowadays, she reflects, patients might sue under similar circumstances

"If you don't have information, you can build pictures in your mind that can affect the way you recover"

until two years ago, was the first hospital-based, dedicated breast cancer charity in the UK, concerned with treatment, supportive care, education and research. "Treat the patient, not just the cancer" was, and still is, its philosophy.

It was one of the first manifestations in Britain of what started to become known as breast cancer advocacy. Its services were, in part, inspired by the American Reach to Recovery Programme, which Freilich visited in 1986 as part of her personal research into how best to offer support to women with breast cancer. It trained carefully selected volunteers – women who had had breast cancer themselves – as counsellors to visit patients in their own homes and support them, their families and friends.

Soon the charity outgrew the one room it had been allocated in the Royal Free Hospital – so another Freilich-coordinated fundraising push resulted in a new Cancerkin centre being opened at the hospital in 1990. It was the first on-site dedicated breast cancer support centre in the UK.

Freilich speaks fondly of the medical staff at the Royal Free – the way doctors supported her ventures throughout, invited her to multidisciplinary meetings and gave seminars to patients and volunteers. But the fact is that in her national work, and the international work that followed, she has had to address a problem that was rife 20 years ago, and still common: doctors did not provide information to cancer patients or involve them in decision-making. More than anything, women like her, and her mother, needed someone to talk to. Freilich acknowledges that it was personal experience that drove her on to correct this.

"The kind of support we offered was completely missing for my mother and me. If you don't have information about a condition, you can build pictures in your mind that can be so harmful and so negative and can affect the way you recover or the way you respond to treatment. But it was unusual for hospital doctors to have much time to spend with patients beyond the hospital environment. The role of the breast care nurse was not very well developed at that time. So I considered it important that patients had someone else to turn to for support.

"I think it's about cooperation. In the past, patients have traditionally deferred completely to doctors, which I believe is wrong. But I don't go along with the idea that women are equipped to make their own independent decisions. They need to be informed sufficiently to be able to make sensible decisions in collaboration with doctors."

Europa Donna

If it was an error that contributed to the founding of Cancerkin, it was a chance meeting that led to Freilich becoming Europa Donna's first president. Her valuable work at the Royal Free led to her being invited onto a Reach to Recovery international advisory committee, under the auspices of the UICC (International Union for Cancer Control) in Geneva. After attending a Reach to Recovery conference in Trieste in 1992, she shared a taxi back to the airport with Umberto Veronesi, and asked him what had happened to his plans to set up a European

With renowned concert pianist Alfred Brendel. Having trained as a pianist and opera singer herself, Freilich put her musical connections to good use, organising fundraisers for Cancerkin. This picture was taken following a Gala Concert featuring Brendel with London's Philharmonia Orchestra, at the Royal Festival Hall, September 2004

breast cancer coalition along the lines of the American National Breast Cancer Coalition. Veronesi admitted that things had not got off the ground as rapidly as he'd wished. Freilich said she was interested in becoming a representative in London, and they exchanged addresses.

Three weeks later, she received a box full of all the papers relating to the proposed organisation. She was kept informed of all correspondence, but didn't have any official role. But a year later, in 1993, she was invited to attend a conference of EUSOMA, the European breast cancer specialists, in Paris. At the end, Veronesi made a surprise announcement: a new breast cancer coalition called Europa Donna was to be formed, and its first president would be Gloria Freilich.

A milestone in patient advocacy. The European Breast Cancer Conference is the first European scientific cancer conference to include patient advocates as equal partners. As Europa Donna president, Freilich was a co-founder of EBCC, and is pictured here at its first conference, September 1998

Nobody was more surprised than Freilich. It took some backtracking – establishing a working party and organising elections – for the body to actually come into being, with Freilich formally at the helm. With enthusiastic representatives of breast cancer patient groups in Italy, Germany, Belgium, Austria, Switzerland and the UK, the objectives were agreed: enhancing the role of women in controlling breast cancer; promoting improvements in the standards of diagnosis and management across Europe; promoting equality of access; making partnerships with clinicians and scientists; influencing European and national politicians. "From the earliest days, we were greatly helped by the valuable support of Alberto Costa and the European School of Oncology, with whom Europa Donna has worked closely throughout its history," stresses Freilich.

The launch conference was held at the European Institute of Oncology in Milan in 1994. "At that time the advocacy concept was barely understood," says Freilich. "Immediately, we had to overcome suspicion of our motives and establish a clear understanding of our mission. We began to make our presence felt through involving ourselves in breast cancer public education, holding conferences and patient meetings, lobbying decision makers, publishing newsletters, holding media campaigns and generally coalition building."

One of Europa Donna's early undertakings – a 15-country survey of women's experiences of breast and gynaecological cancers carried out in 1996 – confirmed the absolute legitimacy of what it was trying to do. "Some of their experiences were pretty ghastly. I think many women felt able, for the first time, to vent feelings they would never have shared with a medical expert. You could tell that people had suffered psychological angst, damage, and the survey drew attention to aspects of treatment and care across Europe where improvements could or should be made."

The fact that Europa Donna – the name is Italian for 'European woman' – was envisaged as a 'sisterhood' is important, says Freilich. It isn't that the organisation has excluded men – supporting male family members and friends is an important objective, and many male clinicians, most importantly Veronesi and Costa, have been influential in driving the organisation forward. "But I suppose that women, by virtue of our biology, have various times of our lives when important events and diseases happen to us alone, and because we have the child

"We had to overcome suspicion of our motives and establish a clear understanding of our mission"

"I did have a very strong feeling about Europa Donna. I thought it would be wonderful to do it"

bearing responsibility, all the gynaecological side of it is more or less out in the open. We're used to communicating with each other about these issues, and even in countries where topics like cancer are not openly discussed, women do get together and support each other in many different ways."

Nevertheless, the fact that breast cancer – and even the breast itself – is still a taboo subject in some countries, has been a consistent hurdle. The original logo design for Europa Donna was a breast, but was vetoed because of sensitivities – instead, it became a map using women's silhouettes. The very word cancer is still barely spoken publicly in some regions – an additional barrier to getting patients to feel confident about talking to others about their condition.

"In some countries, if it becomes widely known that there is cancer in the family, it can cause all sorts of problems, influencing marriage prospects, for example. I suppose it starts with the assumption that if you have cancer, you have an untimely end. That's not necessarily the case any more, and I think that as people acquire confidence about a diagnosis of cancer being properly treated and the possibility of making a good recovery, then fears and superstitions will gradually subside. We are already making a difference."

There have been other significant problems: creating objectives to work towards on a European level has been immensely difficult, given the cultural disparity and variations in health care systems and economies between EU Member States. The idea of patients having a say in their own care is still anathema to some doctors – like the oncologist who stood up to challenge Freilich in 1997.

"Not all countries are readily accepting of laypersons' involvement," says Freilich. "But you change things by driving up levels of understanding and confidence, by encouraging more interplay between the layperson and the medical profession. The medical professionals have to feel confident that they're not going to be overrun by women wildly making demands they can't meet. You change things by showing examples of what has been already achieved, and which they can emulate."

The merits of a professional multidisciplinary approach to breast cancer, which Europa Donna advocates, are still not always appreciated. Wherever this is the case, Europa Donna has had to work hard to persuade medical professionals to link with their colleagues to found multidisciplinary breast units.

But Freilich assesses the organisation's achievements over 16 years as considerable: its influence in the setting of European standards of breast cancer care; its planting of the patient perspective firmly in the centre of high-level clinical and political discussions; the growing acknowledgement of the need for multidisciplinary breast units.

EUROPA DONNA

A powerful alliance. Breast care nurse Sylvia Denton (right) was among the first advocates for patients to be treated by a multidisciplinary breast team, including a specialist breast nurse – key issues for Europa Donna. President of the UK Royal College of Nursing (2002–2006), she is pictured here with Freilich at the Europa Donna conference, Paris 1999, where she led a one-day course on endocrine therapy aimed at nurses from Europa Donna's member states

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A royal occasion. HRH the Duke of Gloucester joined other distinguished patrons, major donors, medical experts and dedicated volunteers for the launch of Cancerkin's 20th anniversary, in Goldsmiths' Hall, the City of London, April 2007

One aim, many cultures

She is proud that Europa Donna membership now extends to 44 countries. She's proud too of the link that she forged with EORTC (the European Organisation for Research and Treatment of Cancer) and EUSOMA to found the biennial European Breast Cancer Conference. And she's certainly proud of the coalition's relationship with the European Parliament.

But she is also realistic. "We wanted to equalise the standard of diagnosis and treatment right across Europe, and one has to acknowledge it's going to be a long time before that happens. We've lately embraced countries like Kazakhstan, Kyrgyzstan and Georgia, and our Russian-speaking Europa Donna Ukraine Forum is able to help them with training and education. But things are going to happen more quickly in some countries than others. Because of these variations, I think there could be more regionalisation within Europa Donna in the future in order to concentrate help where it can be given most effectively."

She sees improving screening as key to sparking developments in all areas of cancer services. "Where good screening programmes have been established, those standards have tended to carry through into surgery and oncology as well," she says. Though there are questions being raised in the UK about how many lives a national breast cancer screening programme really does save, Freilich believes that if the programmes are established to a high standard, and women are provided with quality information about the pros and cons of screening, the benefits outweigh the risks.

Though she is no longer in full-time employment in the cancer world, full retirement doesn't seem an option. The set of oil paints, brushes and canvases she was presented with when she left Cancerkin remain largely untouched, awaiting a day when she has time on her hands. Her work with Europa Donna continues in her capacity as founding president. She remains involved with ESO and many cancer projects, such as the Look Good… Feel Better programme, which provides women affected by cancer with access to cosmetics to address the effects some cancer treatments can have on one's appearance. In 2008 she was appointed a trustee of the Bowel and Cancer Research Trust at the Royal London Hospital, and she would love to see some of the growth in interest and resources that breast cancer has experienced in recent decades spill over into these less well publicised fields.

Was it really chance, luck, mistakes that led her guiding role in these influential breast cancer bodies, as she implies? Her modesty is misleading. The reason behind Freilich's rise in the cancer world becomes clearer when I ask her exactly what it was that Veronesi saw in her, after that conversation in a taxi – what made him want to invest such responsibility and trust in her. She thinks carefully before answering.

"I think he had made some enquiries about my work in London and probably heard a few good reports. I tend to make things happen. I'm a very entrepreneurial person, and I think that if I want to make something happen, and work hard enough at it, I will make it happen. I did have a very strong feeling about Europa Donna. I thought it would be wonderful to do it."

Skill at fundraising, organising people and making alliances, driven by personal conviction. It's a potent combination, which has significantly driven on the cause of user involvement in Europe. It is a combination still vitally needed in cancer organisations around the world.

Future directions in multimodality therapy for NSCLC

Anne Tsao, Jack Roth and Roy Herbst

Patients with stage III non-small-cell lung cancer comprise a heterogeneous population; the role of surgical resection in this setting has been controversial. Albain and colleagues recently demonstrated that trimodality therapy with lobectomy had clinical benefit for patients with pathologic nodal N2 stage III NSCLC.

The role of surgical resection in stage III non-small-cell lung cancer (NSCLC) is controversial, as the population of patients with this disease is rather heterogeneous. Albain et al. reported the results of a phase III trial that compared definitive concurrent chemotherapy and radiation to trimodality therapy with concurrent chemotherapy and radiation followed by surgical resection in 396 patients with pathologic nodal stage 2 (pN2) IIIA NSCLC.[1] The study results suggest that such patients may have a survival benefit from trimodality therapy if a lobectomy can be performed. These findings contradict those reported by van Meerbeeck et al., who did not find a survival benefit for trimodality therapy in any patients with pN2 stage III NSCLC.[2]

The trial by Albain et al. was an international, multicentre study that required pathologic proof of N2 disease, confirmation by a thoracic surgeon that tumours were resectable and exclusion of N3 disease (stage IIIB). In the intent-to-treat analysis, patients who received trimodality therapy had a median overall survival of 23.6 months compared with 22.2 months in the definitive chemoradiation arm (P=0.24). At five years, the absolute difference in survival between the two groups was 7%, in favour of the surgery arm. Although overall survival was not significantly different between the groups, median progression-free survival was better in the trimodality arm (12.8 months vs 10.5 months, P=0.017). The local relapse rate was 10% in the surgery arm, compared with 22% in patients who did not receive surgery, with the greatest effect on relapse achieved at the primary tumour site (2% vs 14%, respectively). Distant

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relapse rates did not differ between the two groups. One of the suggested reasons for the lack of improvement in overall survival, despite the enhanced progression-free survival, was the increased mortality in the trimodality arm after pneumonectomy compared with the chemoradiation arm; 14 of the 16 deaths in the trimodality arm occurred after pneumonectomy, whereas a total of four deaths occurred in the definitive chemoradiation arm. In an exploratory subgroup analysis, patients who underwent lobectomy had a significant overall survival benefit compared with a matched cohort in the chemoradiation arm (33.6 months vs 21.7 months, P=0.002).

The findings of this study have implications for two important surgical issues. First, patients who underwent pneumonectomy (especially right-sided) had significantly worse outcomes than those who were not surgically treated; the exploratory subgroup analysis reported a median survival of 18.9 months for such individuals, compared with 29.4 months in a matched cohort of patients who received chemoradiation alone. One should note that some of these pneumonectomies could have been avoided, as 13 (45%) of the 29 patients whose disease was downstaged to pT0N0 after concurrent chemoradiation had undergone pneumonectomy. Operative mortality with pneumonectomy was 26%. Although these results were from an exploratory matched-pair analysis that was not preplanned, the data suggest that pneumonectomy should be avoided after combined chemoradiation. Other studies, however, have reported much lower operative mortality for pneumonectomy after induction therapy. The reason for this discrepancy among clinical trials is not clear.[3]

Secondly, the trial by Albain et al.[1] supported the use of trimodality therapy in patients with solitary N2 disease who were candidates for lobectomy; however, the benefit was less clear in patients with multistation N2 disease. The subgroup analysis showed improved survival with trimodality therapy only if one N2 nodal station was involved, rather than multistation N2 disease. However, patients whose disease was downstaged to N0 after neoadjuvant therapy had the highest median overall survival (34.4 months); 76 of 164 patients who underwent thoracotomy were downstaged to N0. This finding seems to be independent of the number of nodal N2 stations originally involved before the administration of neoadjuvant therapy and, therefore, supports the use of surgical resection in patients with multistation N2 disease if neoadjuvant therapy accomplishes adequate downstaging. The median survival for patients with residual nodal disease following resection was 26 months, which suggests that these patients may also benefit from surgery if operative mortality is low. Future advances in survival for patients with pN2 stage IIIA disease, therefore, will be dependent on improvements in systemic therapy and in appropriate selection of patients for trimodality therapy.

In addition to defining the role of surgery in patients with stage III NSCLC, this trial also influences the future management of locoregional disease by suggesting that patients with downstaged N2 disease have superior survival. A similar survival benefit in patients with downstaged disease has previously been reported in other neoadjuvant trials.[2,4,5] Use of advanced systemic therapies, therefore, may lead to improved survival outcomes in these patients. Personalised medicine, or the selection of patients for specific systemic therapies, has already been embraced in the metastatic NSCLC setting. This approach could now be incorporated into the management of patients with locoregionally advanced disease, as selection criteria for most trials do not categorise NSCLC beyond disease extent and stage.

In the future, systemic treatment will be optimised according to tumour histology and molecular profiles, with the potential goal of replacing chemotherapy with novel targeted agents to limit toxic effects while improving efficacy. Molecular selection has been incorporated into the management of metastatic NSCLC – the selection of patients with EGFR mutations who are sensitive to receptor tyrosine kinase inhibitors (TKIs) has resulted in improved survival.[6] However, a prior study[7] of unselected patients with stage III NSCLC who were treated with epidermal growth factor receptor (EGFR) TKIs and radiation did not demonstrate a survival benefit.

Whether subgroups of patients with specific EGFR mutations would benefit from EGFR TKI-based therapy, therefore, remains unclear. Recently, patients with NSCLCs that expressed the EML–ALK4 fusion protein were shown to benefit from ALK inhibitor treatment[8], and insulin-like growth factor receptor inhibitors seem to work effectively in patients with squamous-cell-carcinoma histology.[9]

Whether these targeted agents should be administered alone, with chemotherapy, or with radiation therapy as neoadjuvant or combined definitive treatment remains unknown at this time.

The issue of what sequence of administration of therapy is optimal in the trimodality setting remains controversial. The German Lung Cancer Cooperative Group conducted a multicentre phase III trial in 558 patients with NSCLC that compared neoadjuvant chemotherapy with postoperative radiation therapy versus neoadjuvant chemoradiation. This study reported

increased mediastinal downstaging with chemoradiation, albeit without a difference in overall survival between the two arms.[5] Surgery after chemoradiation is more technically challenging than it is after chemotherapy alone, and carries a two- to three-fold higher operative mortality.[2,5] Neoadjuvant chemotherapy followed by restaging and surgical resection in a patient whose disease was successfully downstaged followed by adjuvant radiotherapy to the mediastinum is already commonly utilised in clinical practice. In the era of molecularly targeted therapies, whether bimodality neoadjuvant treatment is preferable to radiotherapy after surgical resection remains to be determined. The sequencing of therapy administration should be explored but only in parallel with identifying predictive biomarkers and utilising the appropriate targeted agents for maximum benefit.

Selection of patients for aggressive trimodality therapy is currently based on clinical prognostic factors, which are not ideal for identifying individuals who would benefit from treatment. Advances in prognostic molecular modelling need to be developed further and incorporated into the clinical management of patients with NSCLC.

One example is the Lung Metagene genomic profiling analysis, which may identify distinct populations of patients with stage IA NSCLC who have a high risk of disease recurrence despite surgical resection.[10]

Other genomic-profiling platforms are under investigation. These prognostic technologies must be incorporated into multimodality trials and validated to optimise therapy and identify patients who might require an aggressive approach to treatment. One potential future scenario would be to reserve trimodality therapy for patients with pN2 stage III NSCLC who have a high likelihood of disease recurrence according to these prognostic models, in whom the high risk of local recurrence would, therefore, justify the potential added risks of surgical resection in trimodality therapy. Patients whose tumours have a favourable prognostic molecular signature would receive definitive concurrent chemoradiation.

Based on the results of the Albain et al. study,[1] we believe that surgical resection (lobectomy) after neoadjuvant chemoradiation in medically fit patients with pN2 stage III NSCLC can be considered as a therapeutic option. Many US cancer centres already incorporate surgery after either neoadjuvant chemotherapy or chemoradiation for patients with pN2 NSCLC. Incorporation of novel targeted agents and predictive biomarkers to personalise systemic therapy is ultimately likely to improve clinical outcomes. Moreover, prognostic molecular models, such as those that involve genomics, may aid tailoring of how aggressive the multimodality therapy should be for each individual patient. These new technologies have the potential to enable further optimisation and refinement of treatment for patients with stage III NSCLC.

Practice point

Surgical resection (lobectomy) after neoadjuvant combined chemoradiation can be considered as a therapeutic option in medically fit patients with pN2 stage III NSCLC.

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Sunitinib versus interferon-α in metastatic RCC

Jason Faris and Dror Michaelson

Motzer and colleagues presented updated results from a multicentre, phase III trial of sunitinib versus interferon-α as first-line treatment for patients with metastatic renal-cell carcinoma. The observed improvement in overall survival for patients treated with sunitinib further establishes this agent as the reference standard for first-line treatment of good-risk and intermediate-risk patients with metastatic renal cancer.

The care of patients with metastatic renal-cell carcinoma (mRCC) has advanced substantially in the past few years, with the approval of targeted therapies including sunitinib, bevacizumab, sorafenib, temsirolimus and everolimus. Approximately three-quarters of renal cancers are clear-cell carcinomas, and most tumours of this histologic subtype have inactivating mutations of the von Hippel–Lindau gene. This inactivation ultimately causes increased secretion of vascular endothelial growth factor (VEGF).[1]

A recent publication of updated results from a randomised phase III trial by Motzer and colleagues has demonstrated that sunitinib improves overall survival compared with interferon-α as first-line therapy in patients with mRCC. Sunitinib is an orally administered, multitargeted tyrosine kinase inhibitor (TKI) that affects multiple receptors, including the VEGF receptor. In two phase II studies of patients with cytokine-resistant mRCC, treatment with sunitinib resulted in overall response rates of 33% and 40%, with a large percentage of patients achieving stable disease or better.[2] Median progression-free survival (PFS) was around 8.8–8.9 months.[2,3] The results of these studies led to accelerated approval of sunitinib by the US regulatory agency, the FDA, in January 2006 for the treatment of advanced kidney cancer.

The phase III trial of sunitinib was an international trial performed in 101 centres, in which patients with treatment-naive mRCC of clear-cell histology were randomly allocated to either six-week cycles of sunitinib (50 mg once daily for four weeks

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followed by two weeks off therapy) or interferon-α (9 million units subcutaneously three times per week).[3] Randomisation was stratified by patients' baseline levels of lactate dehydrogenase, performance status and history of nephrectomy. Patients with a poor performance status, brain metastases or significant cardiovascular disease were excluded. The primary endpoint was PFS as assessed by the Response Evaluation Criteria in Solid Tumors (RECIST). Secondary endpoints included objective response rate, overall survival, quality of life and drug safety. A preplanned interim analysis demonstrated a significant six-month improvement in median PFS for patients who were treated with sunitinib.

Given the improvement in PFS, the study protocol was amended to allow crossover from interferon-α to sunitinib upon disease progression. After an extended follow-up, Motzer and colleagues have now reported updated results, including overall survival.[4] The objective response rates were 47% and 12% for sunitinib and interferon-α, respectively ($P<0.001$). The median overall survival was 26.4 months for sunitinib and 21.8 months for interferon-α ($P=0.051$). The difference in overall survival reached statistical significance ($P=0.0096$) in a multivariate analysis that controlled for performance status, haemoglobin levels, time from diagnosis to treatment, corrected calcium levels, alkaline phosphatase levels, lactate dehydrogenase levels and the number of metastatic sites.

The borderline significance of the *P*-value for the unadjusted overall survival data may have been a consequence of the crossover and administration of post-study treatments. Each of these effects may have obscured the overall survival benefit of sunitinib. The authors attempted to control for these effects by performing exploratory analyses. After excluding the 25 patients who crossed over to the sunitinib arm, median overall survival was 26.4 months (range 23.0–32.9 months) in the sunitinib arm versus 20.0 months (range 17.8–26.9 months) in the interferon-α arm ($P=0.036$). In contrast to the small number of patients who were allowed to cross over, most patients received post-study treatment. Following discontinuation of interferon-α, nearly 60% of patients received alternate therapies, including other VEGF inhibitors, cytokines, mTOR inhibitors or chemotherapy, and more than half of these patients received sunitinib.[4] Once the patients who received post-study treatment had been excluded from the analysis, the difference between the groups in median overall survival became much more prominent – 28.1 months versus 14.1 months ($P=0.003$).

OVERALL SURVIVAL AND PROGRESSION-FREE SURVIVAL ACCORDING TO RISK STATUS

Risk groups	Sunitinib	Interferon-α
	Overall survival (months)	
All risk groups	26.4 (23–32.9)[1]	21.8 (17.9–26.9)
Good risk (*n*=143)	NR[2]	NR[2]
Intermediate risk (*n*=209)	20.7 (18.2–25.6)[3]	15.4 (13.6–18.2)
Poor risk (*n*=23)	5.3 (4.2–10)[4]	4.0 (2.7–7.2)
	Progression-free survival (months)	
All risk groups	11 (11–13)[5]	5 (4–6)
Good risk (*n*=143)	14.5[6]	7.9
Intermediate risk (*n*=209)	10.6[6]	3.8
Poor risk (*n*=23)	3.7[6]	1.2

[1]$P<0.051$. [2]Median overall survival not reached in either group; [3]Hazard ratio 0.787, 95% CI 0.617-1.004; [4]Hazard ratio 0.660, 95% CI 0.360–1.207; [5]$P<0.001$. [6]Hazard ratio and confidence intervals not available.
Abbreviation: NR, not reached

In support of the validity of these exploratory analyses, when a Wilcoxon analysis was performed instead of logrank calculation, the *P*-value was 0.0128. As the Wilcoxon test preferentially weights early events, this statistical test may be more appropriate than logrank calculations, given the observed effects of crossover and post-study treatment.[4] Thus, the adjusted data from the exploratory analyses form a compelling argument for a true overall survival benefit. This argument is particularly relevant when one considers the extended median overall survival of patients in the interferon-α group – almost 22 months,

compared with the historical survival of 13 months before the advent of targeted therapies.[4]

Similar statistical issues were noted in TARGET (Treatment Approaches in Renal Cancer Global Evaluation Trial), which was a phase III trial of sorafenib versus placebo in patients with mRCC who had been treated with prior cytokine therapy.[5] Although a difference in PFS of 2.7 months that favoured sorafenib was demonstrated, overall survival did not differ between the groups (P=0.146). When patients in the placebo arm who crossed over to the sorafenib arm were excluded from the analysis, the difference in overall survival became significant.[5] The median overall survival of patients in the placebo group was more than 15 months, which is longer than the historical survival of patients treated with immunotherapy. This improvement in overall survival of patients in the placebo group might have been related to the effects of crossover and post-study treatment. Similarly, in another phase III trial, patients with mRCC whose disease had progressed on VEGF-targeted therapy were randomly allocated to receive everolimus or placebo.[6] PFS improved by 2.1 months in the everolimus arm, but no difference was observed in overall survival. Since the protocol permitted crossover to everolimus upon disease progression, the lack of an overall survival benefit was not surprising. Allowing patients to cross over to an effective therapy is arguably the only ethical option and, therefore, selection of PFS as the primary study endpoint may be necessary in the context of crossover designs precipitated by increasingly available and effective targeted therapies.

Two phase III studies – Avastin for Renal Cell Cancer (AVOREN)[7] and Cancer and Leukemia Group B (CALGB) 90206[8] indicated significant improvements in PFS for bevacizumab plus interferon-α compared with interferon-α alone. This effect applied to patients in the good-risk group (12.9 months vs 7.6 months in AVOREN, 11.1 months vs 5.7 months in CALGB 90206) and intermediate-risk group (10.2 months vs 4.5 months in AVOREN and 8.4 months vs 5.3 months in CALGB 90206).

The magnitude of the PFS benefit seemed to be smaller than that of sunitinib. However, definitive conclusions about the magnitude of this benefit cannot be drawn until a direct comparison of these two agents is made in a randomised trial. The efficacy of single-agent bevacizumab in the first-line setting merits evaluation, and the relative toxicity profiles of different regimens might influence the selection of first-line treatment.

For poor-risk patients, temsirolimus remains the standard first-line treatment, because of a proven benefit in PFS and overall survival in a randomised, phase III trial.[9] The efficacy of sunitinib in this population of patients remains to be demonstrated. Many patients with poor-risk disease were excluded from the phase III trial of sunitinib, which limited the study's ability to detect a difference in overall survival. Some data suggest sunitinib may be effective in this setting. In an international expanded-access programme, in which 4564 patients with mRCC were treated with sunitinib, 13% (n=582) of participants were considered to have poor performance status.[10] Among evaluable patients in this subpopulation (n=319), the median overall survival was 6.7 months, which compared favourably to historic overall survival in patients with a poor performance status. Poor-risk patients comprised 9% of this group and had a median overall survival of 5.3 months.[10]

Sunitinib seems to improve overall survival compared with interferon-α, a finding that adds to previously published data of superior PFS. Although the statistical significance of the improvement seems to be marginal at first glance, the effect of sunitinib on overall survival is almost certainly underestimated. Sunitinib remains the standard first-line treatment for good-risk and intermediate-risk patients with mRCC, although the availability of multiple other targeted agents highlights the need for continued clinical research.

Areas for ongoing and future investigations include combination regimens, sequencing of targeted therapies, intermittent dosing strategies and incorporation of individualised biomarker and pharmacodynamic profiles to predict response and resistance to therapy.

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

Practice point

First-line sunitinib improves progression-free survival in good-risk and intermediate-risk patients with mRCC, and confers an overall survival benefit compared with interferon-α

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Competing interests: Dror Michaelson declares associations with the following companies: Amgen, Genentech, GlaxosmithKline, Pfizer, Wyeth

NEWSROUND

Selected reports edited by Janet Fricker

Doxorubicin unnecessary for standard-risk hepatoblastoma

➜ New England Journal of Medicine

Cisplatin monotherapy achieved similar rates of complete resection and survival as cisplatin plus doxorubicin in children with standard-risk hepatoblastoma, a recent trial – SIOPEL 3 – has concluded. As had been predicted, there was less toxicity for patients receiving monotherapy.

The International Childhood Liver Tumour Strategy Group 3 (SIOPEL 3) trial represents a continuation of two earlier trials. In SIOPEL 1, investigators identified two pretreatment prognostic factors – intrahepatic tumour extension and lung metastases – when they administered cisplatin-doxorubicin. Based on these findings, they established two pretreatment risk groups: standard risk (tumour confined to the liver and not more than three hepatic sectors) and high risk (tumours involving the entire liver and beyond). In SIOPEL 2 (a pilot study for the current trial), researchers tried cisplatin monotherapy for the first time, using insights from an earlier trial (*JCO* 2000, 18:2665–2675) that showed a multi-agent anthracycline-free regimen was just as effective as cisplatin-doxorubicin, but with no cardiotoxicity. In the current SIOPEL 3 trial, Giorgio Perilongo and colleagues, from the Department of Pediatrics at the University Hospital of Padua, Italy, set out to answer the question of whether doxorubicin could be safely omitted from the treatment of standard-risk hepatoblastoma, and whether cisplatin alone could be as effective as cisplatin plus doxorubicin. A total of 92 institutions from 24 countries were involved in the study.

Between June 1998 and December 2006, after receiving one cycle of cisplatin (80 mg/m2 body-surface area per 24 hours), children with standard-risk hepatoblastoma were randomised to receive cisplatin (n=126) or cisplatin plus doxorubicin (n=129), administered in three preoperative cycles and two postoperative cycles. Standard risk features were defined as tumours entirely confined to the liver, and involving not more than three hepatic sectors.

During the trial, the protocol was amended, and children with alpha-fetoprotein levels of less than 100 ng/ml were excluded because of "mounting evidence of a poor outcome in these patients," write the authors.

The rate of complete resection was chosen as the primary study endpoint, write the authors, first because it allowed them to obtain meaningful data "regarding the treatment of a very rare tumor in a reasonable time frame," and second "because complete resection is the universally accepted, single most important prognostic factor for long-term overall survival and event-free survival in childhood hepatoblastoma."

The rates of complete resection were 99% with cisplatin and 95% with cisplatin plus doxorubicin, with a difference of 3.9% (95% CI 0.3%–8.1%). The three-year event-free survival was 83% in the cisplatin group and 85.5% in the cisplatin-doxorubicin group, and the three-year overall survival was 95% in the cisplatin group and 93% in the cisplatin-doxorubicin group.

Acute grade 3 or 4 adverse events were 74.4 % with cisplatin-doxorubicin compared to 20.6% for cisplatin monotherapy. No differences in toxicity or nephrotoxicity were detected between the two groups.

"The results of SIOPEL 3 are very encouraging," write the authors. "It has long been known that surgery has an excellent success rate in children with hepatoblastoma and that hepatoblastomas are very sensitive to cisplatin. However, the SIOPEL 3 trial shows that a selected group of patients with hepatoblastoma can be cured with a strategy consisting of cisplatin monotherapy administered preoperatively and postoperatively."

The limited number of patients meant that the authors could not statistically prove their conclusion that the two regimens were comparable. However, the similar rates of event-free survival and overall survival "provide support" for the non-inferiority of cisplatin monotherapy, they argue.

Emerging evidence suggests that few hepatoblastomas with pure foetal histologic features and low mitotic rate seem to be curable by surgery alone, and that small-cell undifferentiated histologic features may have a negative impact on survival, regardless of tumour extension. "Therefore, the conceptualization of future clinical trials should take into account the data from all available trials to refine the appropriate therapy for subgroups of patients with limited-extension hepatoblastoma and to properly balance efficacy and long-term toxicity," write the authors.

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Preserving function when treating brain metastases

➜ Lancet Oncology

Patients with brain metastases treated with stereotatic radiosurgery (SRS) plus whole-brain radiation therapy (WBRT) are at greater risk of a decline in learning and memory function than those receiving SRS alone, a recent study has found. The researchers, led by Eric Chang from the MD Anderson Cancer Centers, in Houston, Texas, conclude that their study supports the use of SRS alone combined with close monitoring as the initial treatment strategy for cancer patients newly diagnosed with between one and three brain metastases.

For more than 50 years WBRT has served as the standard palliative treatment for brain metastases, with randomised trials more recently establishing additional benefits when WBRT is combined with surgery or SRS. Chang and colleagues undertook the phase III randomised trial to test their prediction that the learning and memory function of patients who underwent SRS plus WBRT would be worse than that of patients who underwent SRS alone. "We proposed that memory would be likely to be affected by radiation therapy, given the adverse effects of radiation on neurogenesis of the hippocampus," write the authors.

Between 2001 and 2007, patients with between one and three newly diagnosed brain metastases were randomly assigned to SRS plus WBRT (n=28) or SRS alone (n=30). The researchers measured participants' neurocognitive function using a short battery of neuropsychological tests, where the primary endpoint was changes in the memory function assessed through significant deterioration (5-point drops compared to baseline) in the Hopkins Verbal Learning Test-Revised (HVLT-R) assessment.

Results at four months showed that 52% of patients randomly assigned to SRS plus WBRT showed a significant drop in HVLT-R total recall compared to 24% assigned to SRS alone.

Furthermore, at four months there were four deaths (13%) in the group receiving SRS alone and eight deaths (29%) in the group receiving SRS plus WBRT. The median survival for patients in the SRS group was 15.2 months compared with 5.7 months in the SRS plus WBRT group. After one year, 73% of the surviving patients in the SRS plus WBRT group were free from recurrence, compared with 27% of surviving patients receiving SRS alone.

The trial was stopped at four months in accordance with the predetermined early stopping criteria, which specified that if the probability of one treatment arm being better was greater than 0.975 then the trial should be suspended.

"This study provides level 1 evidence to support the use of SRS alone in the initial management of patients newly diagnosed with one to three brain metastases," write the authors. "We recommend that initial SRS alone combined with close clinical monitoring should be the preferred treatment strategy for such patients."

The recommendation comes despite differences in recurrence favouring joint SRS and WBRT treatment. The risks of learning dysfunction, said the authors, outweighed the benefits of freedom from progression. Nevertheless, patients who opt for SRS alone must be willing to commit to close clinical monitoring afterwards. "Applicability of the findings is dependent on the willingness of patients and their physicians to adhere to a schedule of close monitoring, having consistent access to high-quality MRI, having access to a neurosurgical team willing and able to perform salvage resections when indicated, and applying strict physics quality-assurance procedures for stereotactic radiosurgery," they emphasise.

In an accompanying editorial, Jonathan Knisely from the Yale Cancer Center in New Haven, Connecticut, concludes: "The improvement in both quality of life and survival associated with management by SRS alone show it to be the best approach. Nevertheless, exquisitely detailed MRI studies for planning SRS are crucial for the successful adoption of SRS alone."

■ EL Chang, JS Wefel, KR Hess et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncology* November 2009, 10:1037-1044

■ JPS Knisely. Focused attention on brain metastases. *ibid* pp 1024

Long-term follow-up of adjuvant NSCLC trials

➜ Journal of Clinical Oncology

Two large randomised clinical trials of adjuvant chemotherapy following surgery in non-small-cell lung cancer (NSCLC), published in the same issue of *JCO*, yielded, in the words of editorial writer Jean Yves Douillard, "discordant" results. The International Adjuvant Lung Trial (IALT), at a median follow-up of 7.5 years, showed fading effects for adjuvant chemotherapy on survival; while the North American Intergroup JBR.10 trial, with a median follow-up of 9.3 years, demonstrated that survival benefits were maintained.

The best management of early-stage NSCLC is recognised to be surgical resection with curative intent. However, even with complete resection patients remain at significant risk of relapse and death. Recently, three randomised phase II trials and a meta-analysis have shown significant survival benefit for adjuvant cisplatin-based chemotherapy for selected patients with completely resected stage II and IIIA NSCLC. "Long-term follow-up of patients in these trials is critical to assess whether chemotherapy is associated with a sustained survival benefit and to identify any late toxicities that may be attributable to adjuvant therapy," write the authors of the Intergroup JBR.10 trial.

In the larger, IALT, trial, Rodrigo Arriagada and colleagues, from the Institut Gustave-Roussy in Paris, France, randomly assigned 1867 patients with completely resected NSCLC to three or four cycles of cisplatin-based chemotherapy (n=932) or to observation (n=935). Results at a median follow-up of 7.5 years showed a beneficial effect of adjuvant chemotherapy on overall survival (HR 0.91; 95% CI 0.81–1.02; P=0.10) and on disease-free survival (HR 0.88, 95% CI 0.78–0.98; P=0.02). Furthermore, a significant difference was found for overall survival results before and after five years of follow-up (P=0.006).

"Although the initial benefit during the first five years (reduction of the risk of death) was 14%, after five years, the risk of death was reduced by only 9% with adjuvant chemotherapy and this difference was no longer statistically significant,"

comments Jean-Yves Douillard, from Centre René Gauducheau, (St Herblain, France), in an accompanying editorial.

An analysis of non-lung-cancer deaths for the whole period showed a higher mortality rate in the chemotherapy arm (HR 1.34, 95% CI 0.99–1.81; *P*=0.06. "In the IALT trial, the cumulative lung-cancer-related death rate still favours chemotherapy but an excess of noncancer-related deaths occurred in the chemotherapy arm as compared with the observation arm raising the question of a possible detrimental long-term effect of chemotherapy," writes Douillard.

"This analysis not only confirms a beneficial survival effect of adjuvant cisplatin-based chemotherapy during the first 5 years of follow-up but interestingly shows a significant interaction between the treatment effects according to the duration of follow-up," says Arriagada and colleagues, adding that their findings also raise questions about potential negative long-term effects.

An additional noteworthy finding from the analysis, add the authors, is that a major effect is confirmed in terms of reduction of distant metastases in the chemotherapy arm, with the exception of brain metastases. "If this finding is also reported in other cisplatin-based chemotherapy trials, it would argue for exploration of other potential preventive treatment modalities for patients at high risk of brain failure," they conclude.

In the smaller phase III Intergroup JBR.10 trial, led by Charles Butts from the Cross Cancer Institute in Edmonton, Alberta, Canada, 482 patients with completely resected stage IB or II NSCLC were randomly assigned to receive four cycles of vinorelbine/cisplatin (*n*=242) or observation (*n*=240). At a median follow-up of 9.3 years, results showed patients in the chemotherapy arm continued to experience significant survival advantages compared with patients in the observation arm (HR 0.78, 95% CI 0.61–0.99; *P*=0.04). The absolute improvement in five-year survival was found to be 11% (67% for patients randomised to chemotherapy versus 56% for observation).

Subgroup analysis revealed trends for survival according to disease stage. Patients with stage II NSCLC had a significant benefit in survival from chemotherapy (HR 0.68, 95% CI 0.50–0.92; *P*=0.01), while there was found to be no chemotherapy survival benefit for stage IB patients (HR 1.03, 95% CI 0.70–1.52; *P*=0.87). Within stage IB, however, tumour size was predictive of chemotherapy effect. Patients with tumours 4 cm or larger in size derived clinically meaningful benefit from chemotherapy (HR 0.66, 95% CI 0.39–1.14; *P*=0.13), while those with tumours smaller than 4 cm did not (HR 1.73, 95% CI 0.98–3.04; *P*=0.06). Furthermore, in the JBR.10 trial, the authors found no difference between the groups in the rate of death from other causes or second cancers.

"This updated analysis with more than nine years of follow-up confirms a significant survival benefit for adjuvant chemotherapy in early-stage NSCLC. The survival benefit is seen in the stage II patients. No evidence of unexpected late toxicity or increase in second malignancies from adjuvant chemotherapy was observed," write Butts and colleagues, adding that their study represents the longest reported follow-up data of any of the recent adjuvant NSCLC trials.

Longer follow-up in the adjuvant setting is needed, writes Douillard in his editorial, in order to assess cure. He suggests that the discordant results may in part be accounted for by differences between the two trials, including in the way they defined lung-cancer and non-lung-cancer related deaths, and differences in study patient populations, use of postoperative radiation and types of chemotherapy.

With regards to chemotherapy, the JBR.10 trial used only a single regimen of cisplatin and vinorelbine, while patients in the IALT trial received cisplatin, along with one of four drugs (vindesine, vinblastine, etoposide or vinorelbine).

"The choice of drug to combine with cisplatin may be crucial. To date, vinorelbine is the only third generation drug to demonstrate consistent improvement in survival on a long-term basis," writes Douillard, adding that cisplatin and vinorelbine should be the recommended regimen for a durable and reproducible benefit.

■ CA Butts, K Ding, L Seymour et al. Randomized phase III trial of vinorelbine plus cisplatin compared with observation in completely resected stage IB and II non-small-cell lung cancer: updated survival analysis of JBR.10. *JCO* 1 January 2010, 28:29–34

■ R Arriagada, A Dunant, JP Pignon et al. Long-term results of the International Adjuvant Lung Cancer Trial evaluating adjuvant cisplatin-based chemotherapy in resected lung cancer. *ibid* pp 35–42

■ JY Douillard. Adjuvant chemotherapy for non-small-cell lung cancer: it does not always fade with time. *ibid* pp 3–5

BRCA1 mutation raises risk of contralateral breast cancer

➜ Journal of Clinical Oncology

The risk of women with inherited forms of breast cancer developing contralateral breast cancer depends on the age they first developed breast cancer and the type of mutations they inherit. In the largest risk estimates study yet of mutations in breast cancer, German researchers showed the risk to be higher for women with *BRCA1* mutations than *BRCA2* mutations.

It is well known that women with *BRCA*-inherited forms of breast cancer are at an increased risk of developing second cancers later in life, often in the opposite (contralateral) breast. Feeling that a more accurate measure of contralateral breast cancer risk was needed, investigators, led by Monika Graeser, from the University Hospital Cologne, Germany, decided to undertake a study investigating patients' individual risks. The research was undertaken by the German Consortium for Hereditary Breast and Ovarian Cancer, an initiative involving 12 university centres which, in 1996, established a large registry to collect comprehensive genotype and phenotype data on families with suspected hereditary breast cancer.

Altogether 2020 women with unilateral breast cancer, entered on the registry between 1996 and 2008, were included in the analysis, comprising 978 index patients and 1042 relatives.

Results showed that 25 years after the first breast cancer, the cumulative risk for contralateral breast cancer was 47.4% (95% CI 38.8%–56.0%) for patients from families with *BRCA1* or *BRCA2* mutations. People from families with *BRCA1* mutations had a 1.6-fold (95% CI 1.2-fold to 2.3-fold) higher risk of contralateral breast cancer than people from families with *BRCA2* mutations.

Younger age at first breast cancer was associated with a significantly higher risk of contralateral breast cancer in patients with *BRCA1* mutations, with a trend observed for patients with *BRCA2* mutations that was not statistically significant. Among patients with *BRCA1* mutations who were younger than 40 years when first diagnosed with breast cancer, 62.9% had developed contralateral breast cancer 25 years on, compared with only 19.6% among those whose first diagnosis came when they were older than 50. Importantly, write the authors, there was no indication that the risk of contralateral breast cancer levelled off within 25 years following first breast cancer.

"To our knowledge, this study is the first to show that patients from families with *BRCA1* mutations face a significantly higher contralateral breast cancer risk compared with patients from families with *BRCA2* mutations," write the authors, adding that the estimated absolute risks in the study were considerably lower than in other studies. "(This) may be of particular clinical relevance for women trying to decide whether to undergo contralateral prophylactic mastectomy at the time of breast cancer diagnosis," they suggest.

In an accompanying editorial, Judy Garber and Mehra Golshan of Brigham and Women's Hospital comment that the data from Graeser and colleagues suggest that surgeons, in particular, should recognise that patients could be mutation carriers, based on age at diagnosis, family history, ethnicity and histologic features, and offer to refer them for genetic testing as appropriate.

At least as important for more mature *BRCA1/2* carriers, they add, is the fact that the study showed the risk of contralateral breast cancer was less compelling for these patients. "There is less justification for contralateral prophylactic mastectomy for this group, and the ordeal of bilateral reconstruction of greater consequence," they write.

■ MK Graeser, C Engel, K Rhiem et al. Contralateral breast cancer risk in *BRCA1* and *BRCA2* mutation carriers. *JCO* December 10 2009, 27:5887–5892

■ JE Garber, M Golshan et al. Contralateral breast cancer in BRCA1/BRCA2 mutation carriers: the story of the other side. *ibid* pp 5862–5864

Home care nursing improves chemotherapy toxicity symptoms

➜ Journal of Clinical Oncology

Home care nursing (HCN) programmes for patients with colorectal and breast cancer receiving oral chemotherapy both improved symptoms and resulted in reduced use of medical services, reports a UK study.

Capecitabine, an orally administered chemotherapy for adjuvant/metastatic colorectal cancer and metastatic breast cancer, produces toxicity in up to 26% of non-pretreated patients and 45% of pretreated patients. An earlier, separate, systematic review had found evidence for the benefits of home care programmes for patients with incurable cancer to be unclear. In the first supportive care randomised trial to test the effects of interventions in patients receiving oral chemotherapy, Alex Molassiotis and colleagues, from the School of Nursing, Midwifery and Social Work at the University of Manchester, UK, set about investigating whether HCN might be a potentially valuable service to offer patients.

In the study, 110 patients with colorectal cancer and 54 patients with breast cancer who were all receiving oral capecitabine were randomly assigned to receive either a home care programme delivered by a nurse, or standard care for 18 weeks (i.e. six cycles of chemotherapy). Standard care consisted of information about the drug and its adverse effects provided by the clinician and accompanied by written information (with patients provided with emergency hotline phone numbers), while the HCN programme included symptom assessment, patient education and/or treatment of symptoms on the basis of agreed protocols, and one standard home visit.

Significant improvements were observed among patients assigned to the home care group for the first four cycles in relation to oral mucositis (P=0.001), diarrhoea (P=0.031), constipation (P=0.002), nausea (P=0.006), pain (P<0.0005), fatigue (P<0.010) and in relation to insomnia for all six cycles (P<0.0005).

Furthermore, although visits to GPs were similar for the two arms, there were significantly lower numbers of calls to the hospital emergency hotline (32 for HCN vs 91 for standard care, P=0.0005) , lower utilisation of other health care services (35 for HCN vs 74 for standard care, P=0.008) and lower numbers of inpatient days in the home care group (57 for HCN vs 167 for standard care, P=0.02).

"An HCN, symptom-focused intervention appears to be an effective way of supporting patients," write the authors, adding that although this may not be feasible for large numbers of patients who receive oral chemotherapy, resource savings in other areas of health care utilisation might offset the HCN costs.

Improvements in toxicity were most evident in the first two cycles of chemotherapy (i.e. the first six weeks), supported by both the single toxicity score and the analysis of each individual symptom. "This suggests that the most crucial time to provide a supportive care intervention in patients receiving capecitabine is during the first two cycles of treatment. Although patients generally receive information and education about their chemotherapy before starting treatment, they may feel overwhelmed with such information, and re-education and support during the first few weeks of treatment seems an appropriate and useful approach. Also, such an intervention maintains better continuity of care and a more positive experience of treatment," write the authors, adding that the generic approach to symptom management makes this intervention appropriate for other oral chemotherapies.

■ A Molassiotis, S Brearley, M Saunders. Effectiveness of a home care nursing program in the symptom management of patients with colorectal and breast cancer receiving oral chemotherapy: a randomized, controlled trial. *JCO* 20 December 2009, 27:6191–6198

Spreading the word

How patient groups are delivering life-saving messages to all corners of the globe

Peter McIntyre

Cancer patients and their friends and families are uniquely placed to challenge fears and misperceptions that hamper prevention and contribute to late diagnoses, poor treatment and the social isolation of patients. Acting locally but using the Internet to organise globally, patient advocacy groups are extending their support and campaigning work to all corners of the world.

The past decade has seen changes in public awareness about cancer that may be as profound as the changes in treatment. Just as treatment is shifting to a more targeted approach, so too have the voices of cancer become more individual and targeted.

There has been a marked rise in patient-centred groups that reflect the experience of having cancer and the priorities of those who are being treated and who give voice to their concerns and those of their families.

Although there are sometimes disagreements between patient advocacy groups and health policy makers and providers, as these groups have matured, they have generally established good relationships with researchers, the pharmaceutical industry and healthcare professionals with benefits to both sides. Modern health services have come to recognise that patient advocacy groups provide them with a more authentic voice of patients than they can achieve through other forms of consultation.

Patient advocacy groups are increasingly addressing the public directly to raise consciousness of their special needs. In part this may be a drive to attract funds for research, treatment and care, but it is also to do with building public awareness about cancer, in the hope that a better educated public will lead to greater pressure on policy makers and funders to give a higher priority to their particular area of interest.

While many campaigns are national and focused on improving access and services in a single country, the increase in Internet access enables patients and their groups to share experiences and information globally, and to combine local and Europe-wide campaigns.

The over-riding mission of Europa Donna, the European Breast Cancer Coalition, is to ensure that all European women have information about and access to state-of-the-art early detection, diagnosis and treatment of breast cancer. It promotes the *European guidelines for quality assurance in breast cancer screening and diagnosis* and works to ensure that national health systems throughout Europe meet these standards.

Member groups in 44 European countries from Albania to Uzbekistan take part in Europa Donna actions. Its central organisation, based in Milan, has a responsibility to raise awareness Europe wide, as their constitution puts it, "enhancing the power of action by European women to gain control of this disease."

Prevention

As part of their advocacy brief, in 2008 Europa Donna launched Breast Health Day (15 October) to reach out to a younger cohort of women to make them more aware of the growing evidence about breast cancer prevention (www.breasthealthday.org).

Susan Knox, chief executive of Europa Donna, and a patient herself, said, "We had been working for a long time on campaigns dealing with the problems of early detection and treatment, primarily with a population of women aged 40 and over. There was a growing body of epidemiological evidence about the amount of breast cancer that can be prevented by healthy lifestyle choices. There are more than 430,000 new cases of breast cancer in Europe each year. We could avoid and prevent perhaps as much as 30% of these by changing life style."

On Breast Health Day 2009, Arantxa Sánchez-Vicario, the Spanish tennis star who won 10 Grand Slam titles in the 1990s, joined Europa Donna to launch a 'Get More Active' campaign to highlight the 10%–16% of breast cancers that may be due to inactivity. Now in her late 30s, Sánchez-Vicario was chosen as someone who would have a positive impact on younger women throughout Europe.

The campaign was launched with a press conference in Brussels at which Peter Boyle, former Director of IARC, the WHO agency for epidemiological research on cancer, presented the most up-to-date knowledge on breast cancer prevention. Local campaigning was also

Spreading the word. Europa Donna enlisted the aid of international tennis champion Arantxa Sánchez-Vicario (left) and the technology of the 'e-card' to spread the message about how important physical activity is to breast health. Pictured with Sánchez-Vicario are the director and president of Europa Donna, Susan Knox (centre) and Ellen Verschuur (right)

WACHHOLDER PHOTOGRAPHY

"It is also to do with the hope that a better educated public will lead to greater pressure on policy makers"

"These prevention messages can be used by all breast cancer groups as they are applicable everywhere"

carried out in 21 countries to mark Breast Health Day, using pamphlets and posters produced by Europa Donna for its 44 member countries.

The Breast Health Day initiative generated 250 media and blog postings in 22 countries, underlining the impact that a well-planned campaign can have both Europe-wide and in individual countries. From 2010, Europa Donna plans to make the campaign global rather than just European. Susan Knox says, "These important prevention messages can be used by all breast cancer groups as they are applicable everywhere; we would like to help spread them to women and girls across the world."

This hub and spokes pattern of central support and national groups is also adopted by many of the advocacy groups focused on some rarer cancers.

The Max Foundation supports people with chronic myeloid leukaemia (CML) and their associations. It administers a patient assistance programme to bring the life-saving drug Glivec (imatinib) to people in under-resourced countries. Executive director Pat Garcia-Gonzalez is the stepmother of Max Rivarola from Argentina, who died from CML in 1991, aged 17.

Patient power

She sees the local groups in countries and individuals who speak out about their experiences as being at the heart of what the Max Foundation does. "Over the past six years we have been very successful in building patient support meetings and patients' associations in countries where there was no concept of emotional support for cancer patients. We also have now these amazing groups of people who are giving back to the community and living very successful and productive lives and literally changing the face of cancer in their communities."

In 2007, The Max Foundation desig-

Images of hope and determination. Painted by Diogenes and David, CML patients in the Philippines, these pictures (part of the Max Foundation's Colors of Hope Gallery) make a powerful point about how cancer need not stop you leading a productive life – a message still rarely heard in many developing countries

MAX FOUNDATION

"We have now these amazing groups of people who are changing the face of cancer in their communities"

nated the month of October for a 'celebration of life,' and in 2009 raised the profile of its 'Maximize Life' campaign with a Tribute Wall, where families post uplifting messages, and a Colors of Hope picture gallery where patients and family carers use art to express their emotions (www.themaxfoundation.org).

Pat Garcia-Gonzalez says, "We were at the point where we wanted to do two things. One was for each association to know that there are others around the world in a situation that is very similar, doing the same thing they are doing, and the other is for the world to hear how important it is to have access to treatment in developing countries.

"The literature tells you that CML is predominant in males and that the average age at diagnosis is between 55 and 60 years old. What we found in developing countries is that it was a very young population – young guys of 28 to 30 years old in the prime of their lives. We are using the experience of CML to get people to understand that cancer is a real disease in developing countries and it is very important to pay attention to it."

One key aim is to reduce stigma. "We are working in places where 'cancer' is a very scary word. People get fired from their jobs. Your sister is not able to get married if you have cancer. If you can get even one person who is living a very productive life with cancer to get out there and start saying that, then we are changing the way that cancer is perceived. People will be more willing to go to the doctor and that this may lead to early detection and more likely good clinical outcomes."

As an alliance of support, advocacy and information groups for brain tumour patients and carers in different countries, the International Brain Tumour Alliance (IBTA) also recognises country groups as a crucial element.

Co-directors Denis Strangman and Kathy Oliver helped form the IBTA out of personal experience. Denis' wife Marg died of glioblastoma in 2001, while Kathy's son has lived with a brain tumour since diagnosis in 2004. Kathy Oliver believes this shapes the organisation. "Everybody who works for the IBTA is a volunteer, including the two directors, and has hands-on experience of the brain tumour journey, either as caregivers or relatives."

Treatment and support

Kathy points out that many messages central to combating other cancers are not relevant for the 200,000 people a year worldwide who develop a primary malignant brain tumour. "I don't wish to take anything away from these campaigns, but in the case of brain tumours, prevention, screening and lifestyle issues aren't relevant. They attack anybody from tiny babies to the elderly. There is no way you can prevent them because nobody knows what causes them and screening is unrealistic, so it really needs a strong focus on treatment and support."

"The dire prognosis and lack of funding for research, together with misdiagnosis and delayed diagnosis, make this an extremely tough disease."

In 2007 the IBTA launched its 'Walk Around the World' event, with sponsored walks in dozens of countries before or during International Brain Tumour Awareness Week in the autumn (www.theibta.org).

The IBTA encourages the establishment of brain tumour patient support groups in countries where they don't exist. It worked with emerging groups in Zimbabwe, Hong Kong and Lithuania that gain greater awareness through activities like the World Walk. In Zimbabwe, where 180 people joined the walk, Christine Mungoshi, director of the Zimbabwe Brain Tumor Association, appeared on television. She said, "It was a true awareness raising event, as many people were not aware of the impact of brain tumours and also the existence of our organisation."

In one Asian country a philanthropist who had a family member recently diagnosed with a brain tumour saw the walk taking place and immediately offered funding for a brain tumour centre.

The strength of the global coalition is reflected in the World Walk project. In 2009, 182 organisations around the globe supported the World Walk and International Brain Tumour Awareness Week. In total, 38,114 participants in 13 countries walked 226,590 kms, the equivalent of five times around the world at the Equator. They raised the equivalent of 2.5 million euros, all of which is retained by local groups for local brain tumour charities and research organisations.

These organisations don't always have the same priorities. "We recognise that every country is different culturally and that resources vary," says Kathy Oliver. "We encourage and network with them. We don't push a particular message when we know it is not going to be relevant in that country."

The Max Foundation too exceeded its target for this year. It aimed to collect 1000 messages on the Tribute Wall during October, and succeeded in collecting 1500 messages from 54 countries.

They raised the equivalent of 2.5m euros – all retained by the local groups for local brain tumour organisations

BRAIN TREKKING, HONG KONG

A global event for local benefit. The Walk Around the World concept, developed by the International Brain Tumour Alliance, neatly links locally organised sponsored walks to the global goal of collectively covering enough ground to encircle the globe – pictured here is the 2008 'brain trekking' walk in Hong Kong

They worked successfully in India, Malaysia, the Philippines and Chile and made contact with new groups in Mauritius, Cameroon and Azerbaijan. The Henzo group in Kenya organised an event in Nairobi and invited the media and people from the community, and launched themselves as a CML patients' association. "It became something very exciting for us to start to put together this movement of people changing the face of cancer in developing countries," says Pat Garcia-Gonzalez. "I think that the main benefit is that many of these young patient associations in countries where we campaign are able to get visibility."

The internet and social networking

All these organisations have used the Internet and social networking sites to great effect.

The Europa Donna Breast Health Day website (breasthealthday2009.org) features an attractive 'e-card', which combines information about the key health benefits of exercise with some clever graphics of bouncing balls – representing both various breast sizes and various sports activities – and a catchy tune. You can send this by e-mail to any woman to encourage them to become more active; the 'e-card' also encourages the recipient to then forward the message to her own friends.

Between October 2009 and the end of the year, about 5000 e-cards were forwarded in this way to women in 58 countries and many more were sent out directly from the site.

"The e-card to me is one of the most exciting aspects of the programme," says Susan Knox. "Younger people today are really learning through interactive websites so we felt that this would be attractive to younger women and a way for them to communicate with each other. It enables us to reach out with important messages to women across the globe."

Kathy Oliver is also enthusiastic about the potential of new technology to increase the power of campaigns. "We keep finding more organisations each year because more and more people hear about the walk. I don't know how we all survived without the Internet in terms of communication. People read about things

"The main benefit is that young patient associations in countries where we campaign are able to get visibility"

"We like to use human power but we don't believe you have to spend a lot of money to do a campaign"

on the Internet and want to do it themselves. We have people contacting us all the time saying, 'What a great idea, I would like to organise this.' It gathers its own momentum."

The Max Foundation not only uses a website to host its picture gallery and Tribute Wall but also has its own Facebook page to publicise its campaigns. Pat Garcia-Gonzalez says, "We like to use human power, but we don't believe you have to spend a lot of money to do a campaign. A lot of it is about giving a little bit of funding to the groups in the country to organise this event. I think we gave a total of around US$ 15,000 (11,000 euros) to put together 40 events in 22 countries."

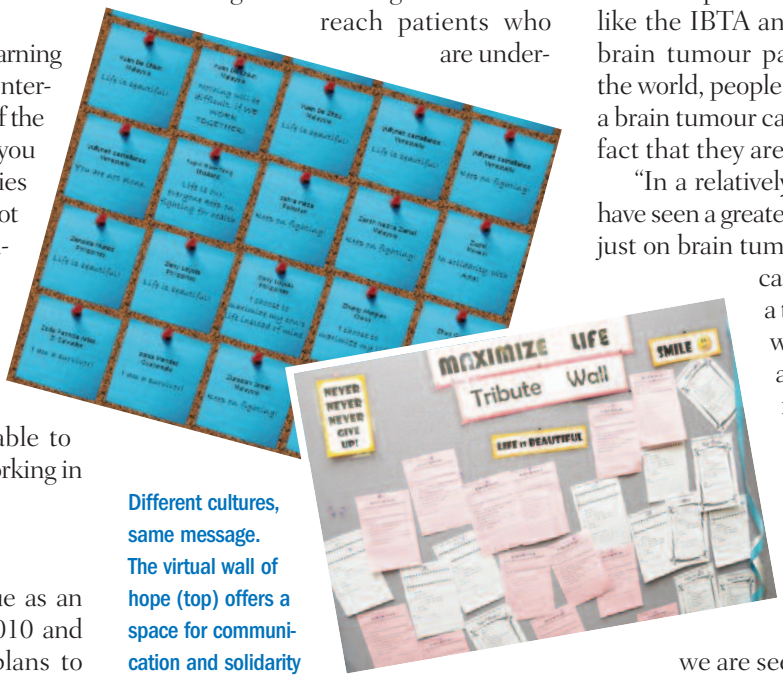
However she has a word of warning about relying too heavily on the Internet and social networking. "One of the big lessons we learned was if you want to do a campaign in countries where access to the Internet is not so broad you have to use a combination of low tech and high tech.

"In these countries, we created a real wall where people put their messages on paper and then we put them onto the Internet. You have to be able to have someone on the ground working in a very old-fashioned way."

The future

Breast Health Day will continue as an annual event on 15 October 2010 and beyond, and Europa Donna plans to extend its prevention campaign globally next year. However, in-depth evaluation will be also be needed, says Susan Knox. "The amount of money we have to spend on a campaign like this is very minimal. The World Health Organization and the European Commission have major prevention programmes, and I would hope that eventually we can link our project with one of these. Otherwise it will be extremely difficult for us to do the kind of studies we would need to measure the impact our programme is having. How many people are changing their lifestyle and how many are even seeing the messages? Those are key questions that need to be answered."

The CML Awareness Campaign will also continue, and The Max Foundation too is looking to combine efforts with larger cancer organisations to reach patients who are underserved. Pat Garcia-Gonzalez says, "We hope to get a little bit more visibility globally, but I am primarily interested in reaching each and every person who can benefit from treatment for CML."



Different cultures, same message. The virtual wall of hope (top) offers a space for communication and solidarity for CML patients and their families with broadband access. Real walls of hope, like this one in Malaysia, are more relevant in many settings (themaxfoundation.org)

The Walk Around the World event will step out again in 2010 – IBTA Awareness Week will be from Sunday 31 October to Saturday 6 November. It is a tool, says Kathy Oliver, both to support individuals and to help change the face of treatment and support.

"When my son was first diagnosed, I knew nothing about brain tumours. My immediate feeling was that we must be the only people in the world who have this problem. Through coalitions like the IBTA and the many excellent brain tumour patient groups around the world, people with a rare cancer like a brain tumour can be comforted by the fact that they are not alone.

"In a relatively short time since, we have seen a greater focus of attention not just on brain tumours but on other rare cancers too. There is still a tremendous amount of work to do in these areas, but we are witnessing the emergence of more targeted therapies, genetic profiling and other cutting-edge aspects of treatment which appear promising.

"What's more, we are seeing increased collaboration on a global scale not just with patient groups but with the scientific community as well – and that is a very powerful direction."