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Learning to care

cancerworld

Kathy Redmond

We need to talk

Cancerworld

Shaping the future of cancer care

Contents

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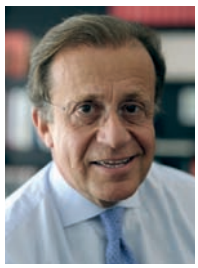


Our keywords

ALBERTO COSTA EDITOR

"Education and knowledge through people and facts" was the strapline that came to me when I got the green light from the Board of the European School of Oncology, and our Sustaining Partners, to launch our own scientific magazine.

I'd had on my mind comments from some of the best students attending our Clinical Masterclass about wanting something that would let them learn more, but in a lighter way: "Something I'm able to read when I'm on my train home or when I'm on night duty," was how one of them put it.

This is how *Cancer World* was born, nearly 15 years ago, appearing initially under the title *Cancer Futures*, published by Springer, and then relaunched under its current title when production was moved in-house.

Under the leadership of Kathy Redmond, a former lecturer and leading light in cancer nursing at University College Dublin, who'd gained extensive policy experience at national and European levels, *Cancer World* quickly grew in competence and confidence.

With thousands of copies distributed by post and at meetings and congresses, the ESO magazine soon established itself as a respected brand that could be found in the offices of countless cancer professionals and in the libraries of most European cancer centres.

Keywords of *Cancer World* include: editorial independence – backed by ESO's own independent financial resources; clinical science – e-Grand Round is the most widely read section; personal experiences – leading figures who shape the world we work in have talked in our Cover Story of the influences that shaped their own careers; and patients' voices – insights and views from the patient advocate community are an essential component of *Cancer World*.

With this issue we wish to pay tribute to Kathy Redmond for that mixture of hard work and inspiration that has earned *Cancer World* a reputation as one of the most reliable and up-to-date oncology publications in Europe.

We plan to build on this success. From January next year, we will increase the number of copies we print to double the number of people who can access this high-quality content. We will continue to seek out significant news in science and medicine, and tell the stories of inspirational people who are making a lasting contribution to improving the way things are done.

At the same time we will address the big challenges in improving access to high-quality cancer care, taking a critical look at the policies, practices and vested interests that stand in the way of making faster progress.

This will be reflected in some design changes to make *Cancer World* slimmer and more nimble. We will also streamline the online magazine with thecancerblog.net and our social media. The heart of *Cancer World* will still be about quality and education. This is an inclusive discussion, and we want more of you to join in. ■

Kathy Redmond
We need to talk

ANNA WAGSTAFF

As founding editor of *Cancer World*, Kathy Redmond set out to open up debate on the future of cancer care in Europe. She started a conversation that a full range of professionals and patient advocates have joined. We are still talking.

"Welcome to our world." When editor Kathy Redmond chose these words to announce the launch of *Cancer World*, the European School of Oncology's magazine, she was not just referring to its title. She was inviting readers to look beyond the boundaries of their own profession, discipline, specialism and status to acknowledge all the people and issues that affect quality of care for patients. She was challenging them to step out of their silos to talk with one another, and she saw the pages of the magazine as a meeting place to work together to achieve more and better.

This was September 2004. The media and journals were full of the promise of the new 'personalised' approach to treatment, using targeted drugs. The search was on for genomic signatures and biomarkers. Treatments were emerging for diseases such as kidney cancer that had seen little progress in survival for decades. There was talk of turning cancer into a chronic condition. A few months later, the publication of two trials of adjuvant use of Herceptin would be greeted with the words, "revolutionary… stunning… and maybe even a cure".

What was missing was coverage of the care received by the majority of patients across Europe who were not in trials or being treated at specialist centres. Stories of patients being failed by services that entrusted their care to

professionals who were not up to the job, working in settings that were not fit for purpose. Stories of health professionals, administrators, policy makers and patient advocates, working to overcome the challenges of inertia, fragmentation and vested interests to improve the way care was planned and delivered. And there was little debate about why change is needed and how best to achieve it.

This was the gap the new magazine was designed to fill.

"It was very important for *Cancer World* to come into being," says Redmond, "because it provided a platform for discussion and debate on key issues impacting on cancer, which did not previously exist.

"*Cancer World* is unique, because of its independence. There are no vested interests, and that allows *Cancer World* to do things that no other magazine or journal could. I was very fortunate, I was given *Cancer World* and told to run with it, because I was in a unique situation that enabled me to ensure that the magazine was not held hostage to any particular line."

A lecturer in nursing at University College Dublin, and still in her early 40s, Redmond had already gained an astonishing amount of experience that gave her insight into the way cancer and cancer treatment impacts on people's lives, and a broad understanding of the factors that impact on quality of care. She saw oncology through a unique lens.

A familar sight. Under Redmond's editorship, leading lights from every corner of the world of cancer were featured on the front cover, making the magazine instantly recognisable

"For me, what was important was to see multidisciplinarity in its widest sense"

She had been elected president of the Irish Association for Nurses in Oncology at the age of 30, and president of the European Oncology Nursing Society (EONS) at 31. When the Irish Minister of Health set up the first National Cancer Forum in 1996, Redmond had been invited to join, on the strength of her advocacy and her profile in Europe.

Her relationship with Alberto Costa, the breast cancer surgeon and director of the European School of Oncology (ESO), led her to leave her native Dublin for Milan. Significantly, ESO had a mandate to reduce unnecessary suffering and death caused by sub-standard cancer care, and had the financial autonomy and independence from any particular professional group to pursue that goal unfettered by vested interests. ESO was looking for new ways to promote the best standards of care just as Redmond, from her new home in Milan, was looking for fresh ways to use her skills and experience, and the unique lens her background had given her.

Thoughtful and provocative

Cancer World is one of the best forums for intelligent conversation about cancer in all its guises and complexity. It explained, argued and led the questioning of major policy issues long before this became in vogue. And it did this in a way that was neither dumb, nor patronising, nor so complex that it was impossible to understand. Kathy has grown *Cancer World* into a thoughtful and provocative title, a place you have to go if you really want to understand the people, politics and policy of cancer.

Richard Sullivan
Professor of Cancer Policy and Global Health at the King's Health Partners Integrated Cancer Centre, London

That is how *Cancer World* was born.

"I was a cancer nurse, so I came with a very different perspective. I was also very involved in advocacy from an early stage. So I came to *Cancer World* with experience of influencing at a political level, and getting policy makers to think about cancer care."

Participating in the National Cancer Forum had taught Redmond to look beyond the training and performance of individual health professionals, to address how cancer services are organised.


SYSTEMS & SERVICES

"At that time, many hospitals across Ireland were treating small numbers of cancer patients without having the necessary expertise. That was how I learnt about the importance of a critical mass: it was only by hearing those discussions, and the discussions about where radiotherapy facilities and specialist services should be located."

Embryonic discussions around the development of cancer services were beginning to take place in a handful of European countries, ultimately leading to the first comprehensive national cancer plans – in England in 2000, Denmark and France in 2003, and Ireland itself, with the National Cancer Control Programme, in 2007. Being involved, says Redmond, was a wonderful learning experience.

"It was very important for me to start to understand what things make a difference in terms of cancer outcomes. It's not just the drug that somebody gets, it's how that drug is given. Does that nurse know how to manage side effects? Does the doctor know what to prescribe? Is there a multidisciplinary team involved? Is the patient being followed up properly? These are organisational issues, separate from the competence of the professional, even though competence is very important."

Redmond came to *Cancer World* with an understanding of the range of people and professions required to plan and deliver cancer care – contributions that were often poorly reflected in the way multidisciplinarity was practised – if it was practised at all.

During her tenure at University College Dublin, she had spent many years on the executive committee of the medical faculty, discussing issues such as training, not just in relation to the medical school but also for other health disciplines including nursing and physiotherapy.

The only nurse "among a crowd of medics", it gave her early experience in advocating for recognition of the value that nursing and other non-medical disciplines contribute to patient care. She would later put that experience to good use, representing EONS on the executive of the Federation of European Cancer Societies (now ECCO).

Looking back, she says, "For me, what was important was to see multidisciplinarity in its

Promoting specialist cancer nursing. The training agreement that still operates between EONS and ESO was first negotiated and signed in 1996, when Redmond held the EONS presidency

A forum for battlers and sufferers

Cancer World has allowed the cancer community to be exposed to unique aspects of this troubling disease. It has created a forum where the human beings that are either the battlers or the sufferers of this disease can truly express their feelings and individual trajectories. This creates a richness, because it highlights the field with perspectives that go beyond science and medicine.

Jean-Claude Soria

Head of early clinical trials and Chair of the Department of Drug Development at the Institut Gustave Roussy, Paris

A link between topics and the cancer community

Cancer World became a unique magazine for the cancer community, as not only does it focus on important cancer topics, but Kathy Redmond has managed to create a link between the cancer topics and the cancer community. Each new issue adds to my understanding of how different professionals from different countries in Europe approach all the aspects of cancer care. It becomes so much more interesting when there is a person behind each story.

Peter Naredi
Former President of the European Society of Surgical Oncologists, and head of the Department of Surgery at the Sahlgrenska Academy, Gothenburg

widest sense. Doctors often have a very limited view of what 'discipline' means."

Redmond also played a leading role in a related campaign – which would later be reflected in the pages of *Cancer World* – to ensure that all the professionals involved in planning and delivering care to patients have the specialist skills they need to do the job properly.

"As an EONS president I was fighting to have specialist cancer nursing recognised. There was a trend towards the generalist nurse, saying that it doesn't matter if you are in an intensive care unit one day, in accident and emergency the next, and in oncology the day after that, because you are a nurse you should be able to nurse.

"I had to fight a few rounds in Brussels, in terms of defending specialist nursing against the generalist position, and this also informed my thinking around the need for competence in all health professionals. It's a safety issue. Patients are exposed to unsafe care if they have an incompetent professional."

Perhaps the single most important formative experience through this period was repeatedly finding that she was the only person speaking from outside a purely medical perspective. Redmond fought, for example, to include a nursing voice in the expert group advising Europe Against Cancer, in which everyone else came from a medical background. "It made me realise that everyone should have a voice, and it is not fair that one group dominates and has the ear of policy makers, because that leads to bad policies."

So by the time she was appointed as founding editor of *Cancer World*, Redmond was clear not just about the topics she wanted to address, but also how she wanted to address them.

"We wanted to help people see the broader issues that impact on cancer care. It was about asking questions about what was going to help save people's lives and their quality of life. Who should have a voice in these discussions? How are these decisions being made? Are we doing this the best way we can?"

She ensured that a full range of voices contributed to the pages of *Cancer World*, in discussions about how to organise services and train health professionals, or about which new therapies and services should be funded, or how research questions should be prioritised

JASON HARRIS

and trial protocols decided. This was not only about including professionals. Redmond established *Cancer World* as a publication where patients and their advocates have a strong voice and gain access to an audience of practitioners and policy makers.

"This is the strength of *Cancer World*," she says. "I wanted it to offer a platform where we are able to give people with different perspectives – not least patients – the opportunity to express positions, and then allow readers to make up their own minds, rather than pushing our own agenda. To me that is a very important approach, because it shows respect for our readers."

'Accurate and critical reporting on cancer can empower people and inform policy'. Redmond, who initiated ESO's media training programme and Best Cancer Reporter Award, is pictured here speaking at the 6th World Conference of Science Journalists, London 2009

Close to patients' needs and expectations

Kathy made *Cancer World* a truly multidisciplinary magazine, which brings us news on who is making a difference, doing what and where, including from the less-visible parts of the world of cancer. I am particularly grateful that she gave visibility to psycho-oncology and psychosocial care. Being a nurse by profession placed her in a privileged position, close to the patients' needs and expectations, focusing on the treatment of the disease but also on caring for the whole person and the human side of cancer. Her wit also did a good service to the magazine, and us all, in making it exciting to read, with a slightly provocative attitude, as it should have.

Luzia Travado
Vice-President of the International Psycho-oncology Society, and Head of the Psycho-Oncology Unit, Champalimaud Clinical Centre, Lisbon

Put in such typically diplomatic language, this may seem a modest enough ambition. But given the medical establishment's long tradition of seeking to conduct most of its business behind closed doors, not to mention the powerful commercial, professional and political vested interests involved in cancer, it takes on somewhat more of an insurrectionary significance.

This is certainly the view of Clifton Leaf, now assistant editor of *Fortune* magazine, whose editorial, Why We're Losing the War Against Cancer [And How to Win it], opened the world of American cancer research to public discussion, a few months before *Cancer World* was launched.

"Don't let that soft Irish lilt fool you," he warns. "Kathy Redmond is a revolutionary. Put a Che Guevara cap on that bouncy blonde bob, stand her at the podium in front of a room of cancer advocates, and you might get an inkling of her rebel soul."

The evidence, he says, is all there in pages of *Cancer World*. "From the outset, [it] reported on matters such as the lack of disclosure in clinical trials registries, the under-appreciation of side effects and the challenges of long-term survivorship, the runaway cost of new drugs and the

The real life stuff

Thanks to Kathy's leadership, *Cancer World* now occupies a unique space. It touches so many critical issues in the field, looking not just at the scientific aspects, but at advocacy, policy, the real life stuff that goes on. I've learnt important lessons, for instance from the story of the woman who was caught between the two worlds of traditional— Western – medicine, and so-called complementary or alternative therapy. I learned about the need to talk ––the two worlds must speak or the patient gets lost between them. And, unlike dense scientific journals, *Cancer World* is a joy to read.

Fatima Cardoso
Director of the Breast Unit of the Champalimaud Clinical Centre, Lisbon

A panel of past presidents. Redmond joined ten fellow former EONS presidents last year at an event to mark the 30th anniversary of the European Oncology Nursing Society, which was held at the Royal Marsden hospital, where it all began

shortages of essential, long-approved medicines, regulatory inertia, gene patents, the perils of overdiagnosis, and more. Rather than shy away from complexity, or strip down weighty problems into bite-size prose, *Cancer World* writers and editors dug deeper – and wrote smarter. They embraced nuance, stood strong in the face of controversy. This was a cultural paradigm shift in oncology-related publishing – and Kathy Redmond led it."

Leaf gives credit, in particular, to the range of voices that were invited to contribute. "Kathy promised from the beginning to give 'voice to health professionals in all fields and at all levels, and offer a platform to those who are most affected by cancer – the people with the disease.' And so she has. In nearly every issue of the magazine, cancer patients themselves have offered insight and perspective to the health professionals who care for them (and sometimes, miscare for them). Much of this ground was uncharted before Kathy's magazine blazed the trail."

After 68 issues Redmond has decided to relinquish her editorial role. "It was an incredible opportunity," she says. "It was very satisfying to be able to put issues on the table that nobody else was going to, whether from fear or just lack of insight."

Some stories ruffled a few feathers, she agrees, especially coverage of debates about

JASON HARRIS

who should be responsible for doing what, and how professional societies should work together. "We take these issues on because nobody else can; nobody else can provide a neutral platform to have those discussions."

The stories she is most proud of are those that explored how doctors and patients can navigate to the best possible outcomes when there are no 'good options' and every choice is ridden with uncertainty. She mentions a 'Patient Voice' story where patients and carers were invited to talk about what they feel constitutes "successful treatment" when a cure is no longer possible, and a 'Cross Talk', where a palliative care specialist challenged a medical oncologist to explain why so many patients continue to be given toxic treatments long after they have any beneficial effect.

One of the great joys of the job, says Redmond, was the feedback from readers. "I was constantly going around, attending conferences, meeting people informally, and it was a great pleasure when people would come and talk about a particular article they had read, or tell me they read the magazine from cover to cover, or say how much they appreciated that we had covered a particular issue."

And certainly, she says, *Cancer World* has helped promote and shape the agenda on improving access to quality care.

"We've always harped on about the importance of quality and audit and the need to measure performance in cancer care. That was a message no one wanted to hear or was interested in 15–20 years ago. Now it's become part of the vocabulary. It's not acceptable anymore just to say we provide a good service; you have to be able to show it.

Patients included as partners

Being 'multidisciplinary' is a widely used concept, but what Kathy achieved with *Cancer World* was including the patient voice, and doing so in a way that placed patients alongside the professionals, not just as equal voices but as partners in the development of cancer care. Finding a top professional like Kathy with a deep intuitive understanding of patients was very refreshing for me.

Roger Wilson

Honorary President of Sarcoma Patients EuroNet, member of the UK National Cancer Research Institute Consumer Liaison group, Shropshire, UK

"If you look at what's happened in breast cancer, that's now starting to happen in other disease areas, where efforts are being made to define not only clinical guidelines, which show how a disease should be treated, but also looking at where they should be treated – the whole issue around specialist units.

"We're seeing much more emphasis on networks and centres of excellence and much more promotion of the message that people have the right to be treated by competent health professionals, and services need to be organised to facilitate that process.

"*Cancer World* pushed this service agenda – saving lives in cancer – and looked at it in its broadest aspect, and also asked the questions about how we can improve patients' quality of life, how we can ensure good deaths."

And there are new challenges. Redmond singles out the projected shortfall in Europe of up to two million clinical and healthcare professionals and long-term care staff by 2020. Who will diagnose, treat and care for Europe's burgeoning population of cancer patients and survivors, many of them frail and suffering other

"We've always harped on about the importance of quality and audit and the need to measure performance"

"There has to be a platform for the community to discuss issues and arrive at conclusions about what to do"

chronic conditions? she asks.

"Cancer is not going away and there are new issues emerging all the time. There has to be some platform for the community to discuss these issues and arrive at some conclusions about how it takes action. Again I'm talking about the broadest community. The cancer community will always have to take action to improve the status quo."

The challenge of bringing new voices to address these upcoming issues now falls on Alberto Costa, who will be retiring from his post as ESO Scientific Director in January 2016 to give more time to his new role as *Cancer World* editor. Costa is keen to build on the magazine's reputation and success by expanding the reach of both its print and online edition and launching a Russian language edition.

Redmond will not be walking away from either patients or the cancer community. "I have been serving patients since I started out in nursing in 1980. And I have served them in different ways, as an educator of nurses, as an advocate, as an editor of *Cancer World*, but always asking the question: how can we make a difference to the lives of individual patients? Now I'm going to do that by helping organisations that serve patients, working with non-profit organisations to help them become more effective and sustainable."

If that sounds like a modest ambition for a woman who has presided over *Cancer World* for 11 years, don't be fooled. Ensuring that the people who have the power to change things listen and act in the best interests of patients will require effective advocacy by organisations serving patients. They will stand a much better chance now they have Che Guevara with a soft Irish lilt on their side. ■

A unique tool for global cancer control

Cancer World has a mixture of a news, science, advocacy and social responsibility agenda, and fills a need by integrating all aspects of cancer. Its multiprofessional, multidisciplinary, and global focus and promotion of integration of clinical practice, academia, and public health make *Cancer World* a unique tool for global cancer control. Kathy is a driving force behind it. She is able to connect with ordinary patients, clinicians, and researchers and hold her own as a global leader, while working for instance on the World Cancer Declaration for UICC and launching and promoting the World Oncology Forum.

I consider her as a 'global cancer treasure' and I am quite jealous that Europe owns her.

Mary Gospodarowicz
Immediate Past-President of the Union for International Cancer Control (UICC) and Medical Director of the Princess Margaret Cancer Centre at the University Health Network in Toronto

Getting serious about biosimilars

VIJAY SHANKAR BALAKRISHNAN & ANNA WAGSTAFF

As patents on the first generation of monoclonal antibodies begin to expire, the cancer community will need to get to grips with the unique issues involved in ensuring the safety and efficacy of copies of these complex drugs made by living cells.

European patents have begun to expire on the first generation of biological anti-cancer drugs.

This should be good news for patients. Opening the market to competitors should help reduce the price tags of monoclonal antibodies, which should in turn give greater access to more patients. It should also generate savings that can be used to help pay for the new generation of biologicals that are now coming onto the market at even higher prices, including immunotherapies.

How far these benefits are realised in practice, however, depends not just on whether one or more competitor drug enters the market, and at what price, but the extent to which they replace the original drug in clinical practice.

Rituximab (MabThera) the first CD20 inhibitor, used in oncology to treat chronic lymphocytic leukaemia and some Non-Hodgkin lymphomas, came off patent in Europe more than two years ago. Cetuximab (Erbitux), the first biological EGFR blocker, used for certain advanced colorectal and head and neck cancers, came off patent in June 2014, closely followed by trastuzumab (Herceptin), the first HER2 blocker, which is approved to treat breast and metastatic gastric cancers overexpressing HER2. The European patent on bevacizumab (Avastin), the first angiogenesis inhibitor, will expire in 2022.

If cheaper copies are to be used in their place, doctors and patients will need to be confident that the competitor can be trusted to offer equivalent efficacy and safety. This raises the same issues of regulatory oversight that are associated with the approval and use of generics, but with an added twist: as biological drugs are derived from living cells, competitor drugs can never be exact copies of the original – which is why they are known as 'biosimilars' rather than 'generics'.

Big money

Exactly how much cancer systems could save by switching to biosimilar monoclonal antibodies remains a matter of speculation, because none has yet been approved for the European oncology market. This is expected to change in the next year or two: Sandoz (a division of Novartis), Hospira (bought by Pfizer earlier this years) and Amgen all have anti-cancer biosimilars in the pipeline, as do

Biological drug facilities. Cells held in these vats secrete industrial quantities of the protein they have been engineered to produce

SCIENCE PHOTO LIBRARY

a number of biologic drug specialists such as the Swiss company BioXpress and Polish company Mabion.

Biosimilars of an earlier, less complex, generation of biological drugs have, however, been routinely used in Europe for almost a decade now. These include the erythropoiesis-stimulating agents (ESAs) epoetin and the granulocytic colony-stimulating factor filgrastim, which are used in oncology as supportive care rather than anti-cancer therapies.

Some evidence is available to show their economic impact, both real and potential.

The German IGES Institute, for instance, has estimated that switching to a biosimilar ESA saved the country around €60 million in the first year. A study based on economic modeling, published last year (*Future Oncol* 10:1599–1609), estimated that potential savings from switching 100% to using a biosimilar ESA across five European countries – Germany, France, Italy, Spain and the UK – could be as high as €146 million, which the authors calculated would be enough to fund the treatment of up to 12,913 additional patients with MabThera, 5171 with Avastin or 4908 with Herceptin.

The question for the future will be how many more people could potentially get access to the latest immunotherapies – such as ipilimumab, nivolumab and pembrolizumab – and other innovative cancer therapies, if and when biosimilar versions of rituximab, trastuzumab and other off-patent monoclonal antibodies come on the European market.

The complexity of manufacturing monoclonal antibodies means that the price difference between the originator drug and any biosimilar is

expected to be smaller in percentage terms than for generics and the first generation of biosimilars. But their high price means that even a small percentage reduction would yield significant savings.

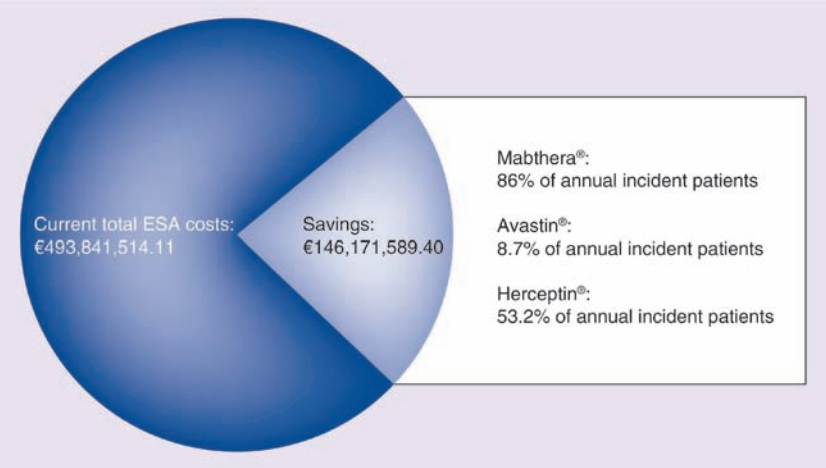
Estimates from the PharmaNano-Gene group at the University of the Basque Country's Faculty of Pharmacy, suggest that introduction of biosimilar monoclonal antibodies could save more than €20 billion across Europe by 2020 (http://tiny-url.com/biosimsavings).

These eye-watering sums could give a welcome boost to efforts to sustain high-quality care for Europe's growing number of cancer patients and survivors.

Achieving anything like that level of savings, however, would require a far greater take up by prescribers than has been seen with the first generation of biosimilars (see below).

This won't happen unless doctors and patients have confidence that any biosimilar approved for the European market is sufficiently similar to the 'reference' drug to be trusted.

OPPORTUNITY COST



Using biosimilars for off-patent biologicals could release funds to pay for innovative drugs. This economic model looked at the German, French, Italian, Spanish and UK healthcare systems and calculated how many additional patients could be funded for biological anti-cancer therapies using money saved by switching to a biosimilar erythropoiesis-stimulating agent

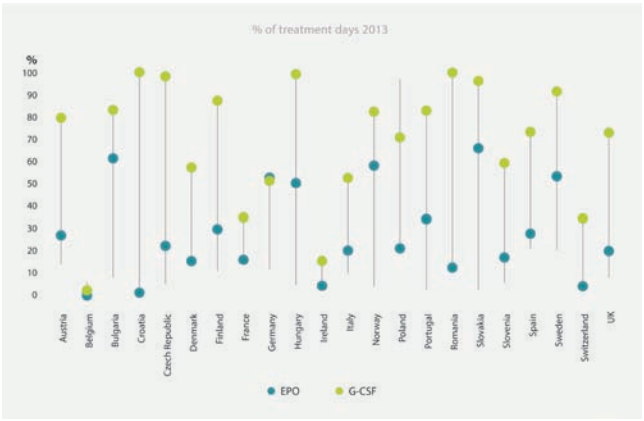
Source: I Abraham, L Han, D Sun et al. (2014) *Future Oncol* 10:1599–1609

How similar are biosimilars?

The regulatory challenge of assessing biosimilars for market approval was first flagged up in 2002 in an article titled "'Biogenerics": the Off-patent Bio-tech Products' (*Trends Pharmacol Sci* 23:119–121). Lead author Huub Schellekens, a professor of pharmaceutical biotechnology at Utrecht University, explains that the complexity arises because biological drugs are derived from living cells, which have natural variations: "Their size and complexity is on a different scale from other types of drug, giving more scope for variations."

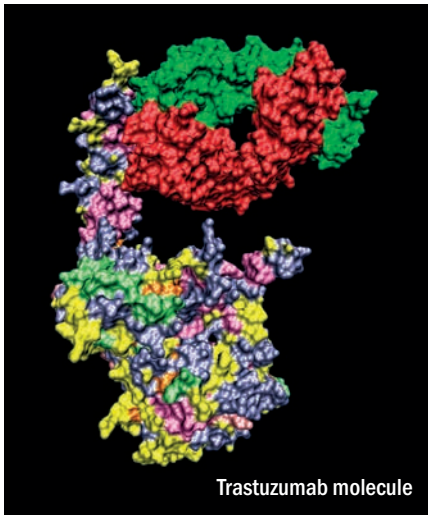
So while trastuzumab and lapatinib both target HER2, the former is almost 150 times heavier than the latter. Complexity of production is another factor, requiring close observation in highly controlled biotechnological labs, often taking many weeks. "It's

USE OF BIOSIMILARS ACROSS EUROPE



Belgium, Ireland, France and Switzerland are the lowest users of biosimilar versions of erythropoiesis-stimulating agents (EPO) and granulocytic colony stimulating factors (G-CSF); Bulgaria, Germany, Hungary, Norway, Slovakia, and Sweden are among the highest

Source: Assessing biosimilar uptake and competition in European markets (2014) IMS Institute of Healthcare Informatics



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very difficult to keep the production conditions constant and homogeneous," says Schellekens.

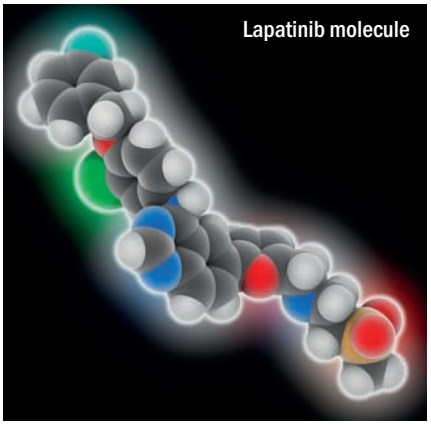
As biological processes are natural, random, and error-prone, the cells that express the monoclonal antibody protein cannot be identical, even in controlled conditions. As soon as cells make a protein, processes beyond the control of any biotechnologist take over.

Schellekens gives an example of the natural addition of sugar molecules to amino acids in proteins, known as glycosylation. "Differences in glycosylation patterns between two batches of the same biologic, for instance, could render them non-identical. Many such complications can modify a protein drug."

Things can go wrong at any stage, from the start of the production process to pharmacist's shelf. As cells spew out biologics, they undergo stresses from acid, heat and other 'crowding proteins' that the cells also produce, potentially leading to structural damage.

The physical and chemical milieu can also affect the next stage of production: extracting and purifying the biologics to obtain a homogeneous batch. Finally, the purified biologic is mixed with inactive ingredients to bring them to a final pill/injectable form. The added excipients, as well as the environment where the drugs are stored, could both act on the biologic drug. "Anything could go wrong anywhere in these steps," says Schellekens.

A different scale of complexity. Tyrosine kinase inhibitors like lapatinib are small and relatively simple molecules, so manufacturing and regulating generic versions is relatively straightforward. Monoclonal antibodies like trastuzumab are large and complex and they can only be produced by living cells, making them more complicated to produce and regulate



But as he points out, these are issues not only for biosimilars, but equally for the original reference drugs, particularly as adjustments are often made to the production process. According to a paper from the Danish health authority, for instance, the manufacturers of infliximab (Remicade), a biologic used to treat conditions including rheumatoid arthritis and Crohn's disease, made more than 35 changes to the production process over 14 years following approval in 1998. These included switching suppliers of cell culture media, moving production sites and introducing new purification steps.

Regulating biosimilars

The complexity of these molecules means that characterising differences between an original biologic and a biosimilar version can only be done through highly sophisticated bio-analytical technologies. The natural variations mean that it is difficult to draw firm conclusions about clinical comparability without seeing evidence that the biosimilar behaves in a comparable manner when used in actual patients.

In addition to quality data showing comparability with the production process of the original drug, and data on how the pharmacokinetics and pharmacodynamics compare, companies are therefore also required to show that their biosimilar demonstrates no clinically meaningful differences, either in efficacy or safety.

This will normally require randomised controlled trials, although not on the scale required for marketing approval of the original innovator drugs. These trials will be looking for equivalence, not superiority, and they will not measure 'hard clinical endpoints', such as survival. In the case of biosimilars for treating solid tumours, for instance, the EMA has indicated that overall tumour response would be a suitable endpoint to demonstrate comparable activity (www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/11/WC500099361.pdf).

There are pragmatic reasons for this. Requiring every biosimilar to jump the same hoops as an originator drug would be unethical, as patients risk losing if the biosimilar is less effective or safe, but have nothing to gain if equivalence is shown. The additional costs of running such trials would also greatly reduce the incentive to manufacturers and potential

"Scientifically, biosimilars are already proven to be safe and effective"

PRINCIPLES OF APPROACH FOR BIOSIMILARS

EMA will require:

- Full quality dossier (covering the chemistry, manufacturing process and controls), including comparisons with original
- Limited preclinical dossier, including pharmacokinetic comparison with original
- Clinical similarity – hard clinical endpoint not needed
- Extrapolation must be demonstrated from one condition to another
- Risk management plan with post-marketing safety studies, including immunogenicity

Source: Adapted from the EMA Guideline on Similar Biological Medicinal Products www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003517.pdf. Last accessed: September 2015

savings to health services. The regulators, both in Europe and the US, insist, however, that, there is also a strong scientific rationale for using endpoints that show a more immediate impact of the drug, arguing that they are less affected by patient- and disease-related factors than are endpoints such as progression-free and overall survival.

One of the big safety issues associated with all biological drugs is their propensity to stimulate an immune response as the body attacks what it identifies as a foreign invader. Such responses could render the drug ineffective – a big concern for patients with a life-threatening disease. They can also be dangerous, as demonstrated in Thailand, where an immune response to copies of epoetin, produced and marketed under the less stringent pharma regulations in that country, led patients to develop pure red-cell aplasia.

Regulators are therefore particularly insistent on seeing clinical data that shows comparability of the immunogenicity profiles. They also require the biosimilar producers to draw up a risk management plan (RMP), just as they would require for an originator. "The RMP for a biosimilar should take into account the identified and potential risks associated with the use of the reference [originator] product and should detail how these issues will be addressed in post-marketing follow-up," an EMA spokesperson told *Cancer World*. The RMP should also include procedures for batch-by-batch quality control after any changes to the manufacturing process.

Such pharmacovigilance is vital in order to trace any clinical issues that arise with respect to both originator and biosimilar drugs, particularly to keep track of their immunogenicity profiles. Links to the periodic safety assessment reports for all products approved from February 2015 are available on the EMA website under the European public assessment reports (EPAR) webpage. RMP summaries for medicines authorised before this date will also be published when variations to their marketing authorisations result in significant changes to the RMP, said the spokesperson.

A question of confidence

Schellekens firmly believes that the regulatory procedures governing the approval of biosimilars for the European market are fit for purpose. A microbiologist by training, he has been a member of the Dutch Medicines Evaluation Board, a national expert of the European Medicine Agency, and a member of the Board of the European Immunogenicity Platform. He has published hundreds of papers in peer reviewed international journals, including on the immunogenicity of protein drugs and the problems related to biosimilars.

"Scientifically, biosimilars are already proven to be clinically safe and efficacious. Only political and bureaucratic caveats exist in communicating their true potential," he argues. Indeed he believes that the current pharmacovigilance requirements, based on spontaneous reporting of adverse effects, may place an unnecessary burden on biosimilar producers, which could push up the price.

He would prefer to see dedicated pharmacovigilance to look for defined effects such as immunogenicity, to narrow the time to trace back any issues. The money spent on expensive RMPs and EPARs could then be channeled into educating physicians and patients, he says.

While educating professionals, patients, policy makers and the public

about the science and related regulatory issues will no doubt be important in building confidence and trust in biosimilars, that still leaves some outstanding concerns.

When is it OK to extrapolate?

The issue of extrapolation is a case in point. Can a biosimilar approved on the basis of clinical data from patients with one indication also be approved for use in other indications for which its reference drug is approved, without actually being tested in these other patient populations?

In an article published last year in *Blood* (vol 124, pp 3191–96) Martina Weise, vice-chair of the EMA's Biosimilar Medicinal Products Working Party, explained the EMA's approach to extrapolation: "If a biosimilar producer establishes the relevant mechanism of action of the biologic and its target in the human body, such as a receptor that receives the biologic, then extrapolation is usually not problematic." Each case needs to be carefully considered on its own merits, however, an EMA spokesperson told *Cancer World*, "and therefore the possibility for extrapolation is limited and needs to be fully justified."

The EMA's judgement on what is justified has been questioned, however, by the European Crohn's and Colitis Organisation, which is unhappy with the 2013 EMA decision to include Crohn's disease and ulcerative colitis among the indications for which Rensima, a biosimilar version of the anti-inflammatory biologic Remicade (infliximab) was approved. Rensima had shown clinical comparability with Remicade in reducing the rate of progression of joint damage in patients with rheumatoid arthritis, and was subsequently approved for treating patients with rheumatoid arthritis, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and Crohn's disease.

The EMA clearly felt that extrapolation from the clinical studies done in rheumatoid patients was justified. However, in a position statement published on the Genetics and Biosimilars Initiative website (www.gabionline.net), the European Crohn's and Colitis Organisation asserted that: "… the use of biosimilars in IBD patients [patients with inflammatory bowel disease – i.e. Crohn's disease or colitis] will require testing in this population with comparison to the appropriate originator product. Clinical efficacy in IBD cannot be predicted by effectiveness in other indications such as rheumatoid arthritis."

Last year the Canadian regulator decided against using clinical data from patients with rheumatoid arthritis as a basis for approving Rensima for treating Crohn's disease or ulcerative colitis, "due to differences between Rensima and the reference product that could have an impact on the clinical safety and efficacy of these products in these indications," though it did approve the biosimilar for ankylosing spondylitis, psoriatic arthritis and psoriasis. The US regulators have currently postponed their decision, pending further information.

Similar controversy could potentially arise with the first rituximab biosimilars, over whether demonstrating clinical comparability in shrinking lymphoma tumours can be extrapolated to indicate comparability in treating rheumatoid arthritis. Schellekens points out that unless there is a strong scientific rationale for a separate trial, the added development costs would push up the price for the rituximab biosimilar with no good reason.

Are biosimilars interchangeable?

Another area where doctors and patients may seek reassurance is over whether biosimilars can be considered interchangeable with the originator drug. Would doctors be able – or be required – to switch patients from the original drug to its biosimilar, be able to switch patients back again, or even switch between biosimilars?

Would pharmacists – or patients – have the right to substitute the biosimilar if the prescription was for the originator drug? Karen Van Rassel, CEO of the patient advocacy group Lymphoma Coalition, says patients are still looking for clarification.

According to Pekka Kurki, at the Finnish Medicines Agency (Fimea), it is not within the EMA's remit to provide that clarification. Addressing a joint meeting of Patients' and Consumers' Organisations (PCWP) and Healthcare Professionals' Organisations (HCPWP) at the EMA, earlier this year, he said "EMA thinks it does not have the mandate on interchangeability because it comes very close to substitution, which is a national issue."

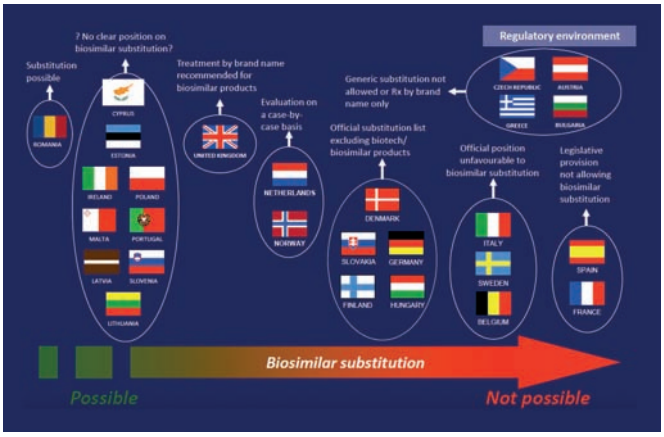
The problem is, as he adds, that

The EMA's judgement has been questioned by the European Crohn's and Colitis Organisation

very few national bodies have issued official recommendations on the interchangeability of biosimilars (see figure).

Matti Aapro, Dean of the Multidisciplinary Oncology Institute, in Genolier, Switzerland, has been studying and administering biosimilars for many years, in his capacity as a medical oncologist specialising in supportive cancer care. He argues that there are no grounds to believe interchanging between innovator products and biosimilars could create problems. "There is no scientific evidence at all that there is a biological or clinical risk if you change from one product to another," he says. He agrees, however, that if a patient or a pharmacist wishes to interchange between an originator product and a biosimilar, or between biosimilars, for reasons of cost, they should do so with the knowledge of the prescribing physician. "Physicians should keep stringent records on any interchange, switch, or substitution, so that if any problem occurs due to this change, the issue can be traced back."

BIOSIMILAR SUBSTITUTION POLICIES



Policies on whether biosimilars can be substituted for a prescribed innovator drug vary widely, with many countries still having no policy at all

Source: Courtesy of Huub Schellekens

Transparency and the battle for perceptions

The principle of transparency – that professionals and patients should always know whether a given drug is the original or a biosimilar – is widely recognised as a cornerstone of building confidence in biosimilars. Exactly how that should be reflected in the way they are named, however, remains a matter of controversy.

There is agreement that each biosimilar should have its own brand name or unique identifier, but should it be allowed to share the same 'generic' or 'international non-proprietary name' (INN) as the innovator product? Should a biosimilar of Herceptin go under the INN 'trastuzumab', or should its INN carry a 'biological qualifier' eg a suffix that indicates the drug is a biosimilar, or identifies the company that made it? Arguments centre on the potential for confusion and error.

Adding a suffix, some argue, will reduce the likelihood of inadvertent and inappropriate product switching and strengthen the accuracy of tracing via post-marketing safety monitoring systems. Others suggest, however, that the system of brand name plus INN is a worldwide system that works well, and adding a layer of complexity will actually increase the chance of errors.

While these concerns are legitimate, they also act as a surrogate for a battle over perceptions. Adding a qualifier to the INN sends out a signal that the biosimilar is not really a version of the same drug. Using the same INN conveys the opposite. Perceptions are likely to have a significant impact on the extent to which biosimilars are adopted into clinical practice.

In August 2015, the FDA published its long-awaited guidelines on the naming of biosimilars, coming out in favour of a suffix.

The recently approved biosimilar for Amgen's Neupogen – INN "filgrastim" – has accordingly been given the INN "filgrastim-sndz", to indicate it is a biosimilar manufactured by Sandoz.

Europe, in contrast, seems to be leaning towards using identical INNs. Concern that a different INN for biosimilars "could undermine the trust of healthcare professionals and the public" was one reason put forward in favour of this position, according to minutes from the October 2013 meeting of European Commission's Pharmaceutical Committee.

This is not unreasonable, given the €20 billion that some projections estimate could be saved across Europe by 2020 with a 100% switch to biosimilar monoclonal antibodies. But if Europe is going to achieve even a 50% switch rate, policy makers will not be able to rely on identical INNs to command public and professional confidence. They will need to build that trust not just through education, but also by listening to the concerns of the cancer community, and convincing them that the EMA approach to the regulatory challenge posed by biosimilars is scientifically sound. ■

Asking the value for money questions

SIMON CROMPTON

Delivering the best possible quality of cancer care to every patient requires getting value for money from scarce resources. BBC journalist Matthew Hill earned himself a Best Cancer Reporter Award for taking a critical look at the cancer spending priorities in England.

Good journalism springs from asking the difficult questions that others are reluctant to publicly address. Matthew Hill, winner of this year's ESO Best Cancer Reporter Award, tackled a topic that may be increasingly discussed behind closed doors, but rarely gets a wide airing: "Is cancer money well spent?"

According to Hill, a BBC health correspondent in the West of England for 20 years, journalists who want to provide an objective and well-informed perspective on cancer and cancer care have a big problem. Everyone they speak to seems to have a vested interest.

"Coverage of cancer can be dangerously skewed by the press releases journalists receive," says Hill, who has reported for national BBC television and radio programmes, including *Newsnight*, BBC News and *Panorama*. "You're not given the full facts, and as a journalist you're quite conscious of being manipulated by people with a vested interest – particularly in the field of drugs."

For example, Hill says he regularly receives press releases and emails from local consultants calling for certain drugs to be approved for reimbursement by the National Health Service. However, careful analysis of the evidence reveals a complex picture, where cost is major, benefits marginal and side effects significant. This is rarely if ever presented to journalists. They need to do their own digging and assessing.

The problem was a motivating factor behind one of the two reports Hill submitted for this year's European School of Oncology Best Cancer Reporter Award, presented annually to recognise intelligent and critical cancer coverage.

"It struck me as important to stand back a bit and look at the rationale for the decisions made about cancer spending," he says. Hill made

Award winner. Matthew Hill conducting an interview for BBC television at the 2015 European Cancer Congress, Vienna

PETER MCINTYRE

a 40-minute report for BBC Radio 4's Science Unit entitled "Is Cancer Money Well Spent?", broadcast on 12th April 2015.

Its starting point was a cancer patient in Somerset – Hill says patients are the source of many of his stories. Doctors believed she would benefit from a new type of stereotactic radiotherapy which was not available in the UK – even though it is commonly used in other European countries. This led Hill to ask whether the £6 billion (just over €8 billion) spent on cancer in the UK every year was being used effectively to embrace the best in radiotherapy and surgery as well as drugs.

And given that one in two of us will receive a cancer diagnosis in our lifetimes, was enough being spent on prevention and early diagnosis – for example through genetic testing?

His interest broadened after he attended a palliative care conference and was astonished to hear evidence that good-quality palliative care not only improved quality of life, but can also extend duration of life. "Should we be investing in

this relatively cheap area, instead of some cancer drugs costing tens of thousands of pounds?"

His investigation took him to interview cancer patients, doctors in France (where survival rates are higher than the UK), academics and consultants in Bristol. He also spoke to Richard Sullivan, Director of the Institute of Cancer Policy at King's College London, who pointed out that the £2 billion (€2.75 billion) spent on cancer medicines in the UK result in only a 2–4% improvement in population survival across all cancers. Sullivan highlighted the need to build international registries, documenting the actual long-term benefits of all cancer treatments.

At the end of his report, Hill concluded: "Evidence would suggest that, in terms of survival and cure, front-loading the system is most effective – better diagnosis, optimum surgery and radiotherapy. But realistically there will always be people who are diagnosed at the late stages of the disease, and we'll always need to be aware of new innovative treatments.

"The silver bullet for cancer remains elusive for scientists, doctors and patients alike, so we are left juggling. But if we were designing a cancer system we probably wouldn't start from where we are now."

Hill's determination to get to the bottom of difficult questions hasn't been limited to cancer. As a BBC health correspondent he broke the story of alarming mortality rates among child heart patients in Bristol in 1995, and has investigated how patients are swindled into paying for gastric banding and unproven stem cell therapies.

PETER MCINTYRE

Thanks BBC. Receiving his award from Fedro Peccatori, ESO's Deputy Scientific Director, Hill paid tribute to the BBC for giving journalists the time they need to investigate complex topics

But he has always been interested in cancer, and this gained a personal impetus three years ago when his younger sister died of a brain tumour. "I wouldn't say it's changed what I did, but it's focused my mind, onto research in cancer primarily."

Hill's second entry to the Best Cancer Reporter Award was a television report for the BBC *Inside Out West* programme. Hill secured exclusive access to one of the first patients in the world to receive an experimental technique of feeding chemotherapy drugs directly to an inoperable brain tumour via surgically implanted catheters.

The experimental treatment was developed by neurosurgeon Steven Gill at Bristol Royal Hospital for Children. Hill accompanied 17-year-old James Willetts and

"As a journalist you're quite conscious of being manipulated by people with a vested interest"

Hill would like to see more efforts to look beyond the limited perspectives of different cancer disciplines

his family through the journey of implantation and treatment. The judges for the Best Cancer Reporter Award liked the piece because of the way it reflected the personal experience of undergoing experimental treatments from both the patient and professional side.

Hill is all too aware, however, of the dangers of raising false hope by focusing on one innovative treatment. "Professor Gill's work seemed such a radical development, and one that could lead to further breakthroughs, so it was worth following the patient. But I know what it's like to have false hope raised. The genetic sequence in my sister's glioblastoma meant that she was eligible to receive the drug Glivec on a compassionate basis. This was experimental, but it didn't work for her."

Journalists have a responsibility to use phrases such as "early stages" and "highly experimental" when describing trials, he says. "The headlines will always be there because we want people to pay attention, but you've got to get the details in to the report explaining the full situation, and hope that the public will take it in."

What would improve standards of reporting on cancer internationally? Hill would like to see more efforts in Europe to look beyond the limited perspectives and vested interests of different cancer disciplines and professions. "There are very few bodies that stand back and provide commonality, and a consensus on different types of treatment," he says.

In accepting his award, which was presented to him at the 2015 European Cancer Congress in Vienna, Hill said he appreciated it as much for the recognition it gives to the BBC as to himself. At a time when the funding, organisation and remit of the BBC are themselves undergoing scrutiny, Hill is acutely aware of how few news outlets and organisations allow journalists the luxury of actually investigating topics – rather than relying on those press releases and partial opinions that can provide such a skewed version of reality.

"The BBC gives me the time to do this kind of research," he says. "That comes with being a public service organisation, This award recognises that, and the fact that there aren't many media outlets that allow that freedom." ■

PETER MCINTYRE

Sharing tips and experiences. Hill contributed to a session on reporting on service priorities and value for money, held as part of the Reporting on Cancer training course run by ESO for European health journalists at the 2015 European Cancer Congress

Managing common toxicities with new tyrosine kinase inhibitors

TKIs are involved in treating an increasing number of cancer indications. Doctors need to be aware of the range of potentially serious side effects associated with these drugs, and know how to mitigate them, to ensure that their patients get the greatest benefit.

A large number of tyrosine kinase inhibitors (TKIs) targeting specific receptors have been approved over the last five years for many different types of cancer.

These agents inhibit kinase enzymes that act as 'on' or 'off' switches in many cellular activities, including proliferation, apoptosis, metabolism and transcription.

Different classes of TKIs targeting specific receptors are typically associated with particular toxicities (see figure overleaf):

- EGFR inhibition is generally associated with skin rash, diarrhoea, mucositis and, less frequently, pneumonitis.
- VEGFR inhibition leads to hypertension, proteinuria, wound healing complications, hand-foot skin reaction (HFSR) and also some vascular complications such as arterial thromboembolism and left ventricular dysfunction.

European School of Oncology e-grandround

The European School of Oncology presents weekly e-grandrounds which offer participants the chance to discuss a range of cutting-edge issues with leading European experts. One of these is selected for publication in each issue of *Cancer World.*

In this e-grandround Mafalda Oliveira, from Vall d'Hebron Institute of Oncology in Barcelona, reviews the common toxicities that occur with novel tyrosine kinase inhibitors, and discusses the implications for providing optimal care for patients being treated with these drugs.

Edited by Susan Mayor.

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

'NEW' FDA-APPROVED TKIs AND THEIR INDICATIONS

Lenvatinib* (Feb 2015)	Differentiated advanced thyroid cancer refractory to I-131
Nintedanib (Oct 2014)	NSCLC, in combination with docetaxel, 2nd line
Ceritinib* (Apr 2014)	ALK+ metastatic NSCLC, progressed on or intolerant to crizotinib
Afatinib* (Jul 2013)	NSCLC EGFR exon 19 del / exon 21 L858R substitution gene mutation
Ponatinib* (Dec 2012)	Chronic, accelerated, and blast phases of CML and Ph+ ALL resistant to other TKIs (especially CML with T315O mutation)
Cabozantinib* (Nov 2012)	Metastatic medullary thyroid cancer
Bosutinib* (Sep 2012)	Chronic, accelerated or blast phase Ph+ CML who are resistant or intolerant to other therapies, including imatinib
Regorafenib* (Sep 2012)	Colorectal cancer late line
Axitinib* (Jan 2012)	Advanced renal cell carcinoma second line
Ruxolitinib* (Nov 2011)	Intermediate / high-risk myelofibrosis Polycythemia vera if PD / intolerance to hydroxyurea
Vandetanib* (Apr 2011)	LA/metastatic medullary thyroid cancer (especially RET mutation)

NSCLC – non-small-cell lung cancer, Ph+ – positive for the Philadelphia chromosome translocation, CML – chronic myeloid leukaemia, ALL – acute lymphoblastic leukaemia, PD – progressive disease, LA – locally advanced, *also approved by the EMA

Source: Adapted from www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm279174.htm (viewed 6 October 2015)

- HER2 inhibition is associated with diarrhoea and rash, which are the most common toxicities associated with TKIs, and may also cause left ventricular dysfunction.
- ALK inhibition is most commonly associated with gastrointestinal toxicities such as nausea, vomiting and diarrhoea, some laboratory abnormalities such as elevated aspartate aminotransferase (AST) and alanine transaminase (ALT) and, less commonly, pneumonitis.
- BCR-ABL kinase inhibition typically causes cytopenia, in addition to cardiac abnormalities and hypothyroidism.

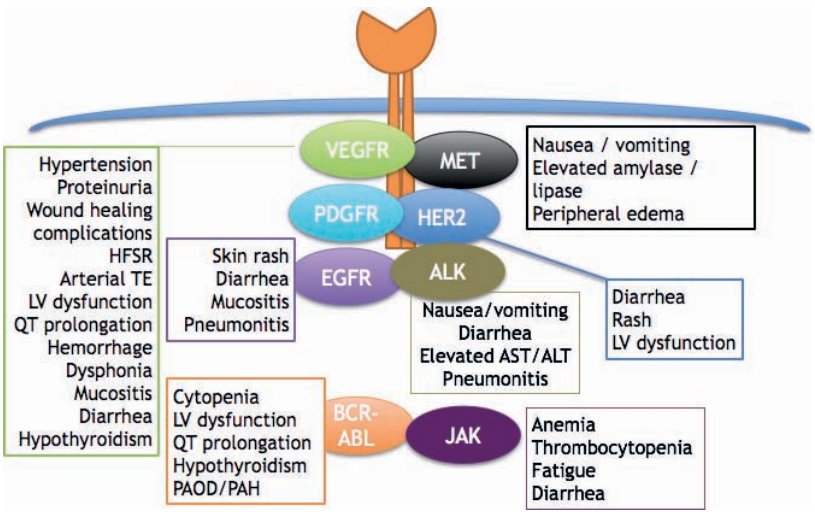
EGFR inhibitor-associated toxicities

Rash, diarrhoea and mucositis are very common toxicities with EGFR TKIs. Rash is one of the most common toxicities in patients treated with EGFR inhibitors. Results for the adverse event profile in the LUX-LUNG 3 study that resulted in the approval of afatinib in non-small-cell lung cancer (NSCLC) showed that 89% of patients treated with the agent developed rash, with 16% having rash that was grade 3 or higher (*JCO* 2013, 31:3327–33). Other common side effects of afatinib were: diarrhoea (95% of patients), stomatitis (72%), paronychia (57%) and dry skin (29%).

Rash with EGFR TKIs

Skin adverse effects with EGFR inhibitors are very common and we must be aware of them to improve the care of our patients. The figure opposite shows the grades and different types of rash associated with EGFR inhibitors. Several types of rash can occur, including acneiform or pustular rash (*left*) but rash can also have a more generalised distribution and be maculopapular (*centre*). Rash can also be triggered by sun exposure, resulting in a photosensitivity rash (*right*). Acneiform rash is the type of rash most com-

OVERVIEW OF TOXICITIES ASSOCIATED WITH DIFFERENT TKI TARGETS



monly associated with EGFR inhibition. It is defined as the eruption of papules or pustules and typically occurs on the scalp, upper chest and back. It improves over time if medication is continued, and resolves fully when treatment is discontinued.

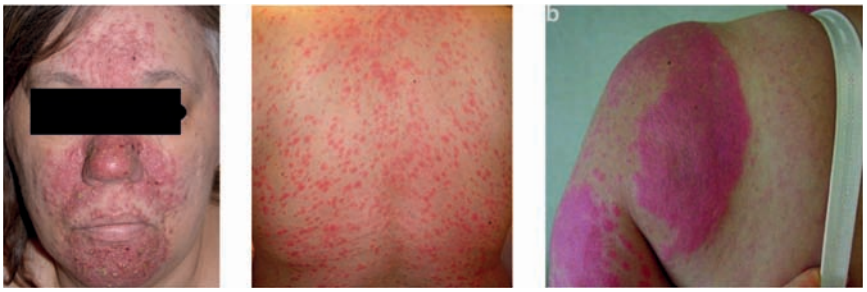
All treatment-related toxicities in clinical trials are rated according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events, and this is also useful in clinical practice. These criteria use the body surface area affected by rash as the main parameter to discriminate between the different grades: up to 10% for grade 1; 10–30% for grade 2, which may also have associated symptoms; and more than 30% for grade 3 rash, which limits self-care activities and may also be associated with local infection.

However, there are some limitations to using these criteria to classify EGFR TKI rash. Typically, in terms of assessing body surface area affected, EGFR-associated rash occurs on the face, trunk, scalp and the upper torso, and the NCI criteria do not take into account the severity of rash complications, such as oozing, burning, crusting or disfigurement. These are important factors to consider in order to give appropriate medication and in making decisions on when to stop EGFR inhibitor treatment or lower the dose.

Before initiating EGFR inhibitor therapy, several preventive measures can reduce the risk of skin rash. Areas of dry skin should be moisturised twice daily, because good hydration can prevent TKI-associated rash. Patients should minimise sun exposure and use a sunscreen with a protection factor of at least 15 to prevent photosensitivity rash. Patients should also avoid products that dry out or irritate the skin, such as soaps or alcohol-based perfume products.

The figure overleaf shows a composite of several treatment frameworks for managing TKI-associated rash. The dose of EGFR TKI should be changed only in patients with grade 3 rash. For patients with grade 1 or 2 rash, I usually continue EGFR treatment and use topical treatment for their rash. Patients with mild skin rash may need no intervention, but topical hydrocortisone or clindamycin are reasonable options even if the rash is only grade 1.

GRADES AND TYPES OF RASH WITH EGFR TKIs



Grade 1	Papules or pustules, or both, covering less than 10% of body surface area, which may or may not be associated with symptoms of pruritus or tenderness
Grade 2	Papules or pustules, or both, covering 10%–30% body surface area, which may or may not be associated with symptoms of pruritus or tenderness Associated with psychosocial impact Limits instrumental activities of daily living
Grade 3	Papules or pustules, or both, covering more than 30% body surface area, which may or may not be associated with symptoms of pruritus or tenderness Limits self-care activities of daily living Associated with local superinfection, with oral antibiotics indicated
Grade 4	Papules or pustules, or both, covering any percentage of body surface area, which may or may not be associated with symptoms of pruritus or tenderness and which are associated with extensive superinfection, with intravenous antibiotics indicated Life-threatening consequences
Grade 5	Death

Source: Adapted from Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0

Topical hydrocortisone or clindamycin should be used to treat grade 2 rash, and oral antibiotics such as doxycycline or minocycline should be considered if patients have pustules or are beginning to develop an infection. Similar topical and oral treatment should be used in patients with grade 3 rash, with the addition of a short course of oral corticosteroids (typically 10–14 days) if the rash is really troublesome. Patients with EGFR-induced rash should be reassessed after two or three weeks of treatment and offered the next step in treatment if the previous therapy has failed to control the rash.

EGFR TKIs have long half-lives, so the management of adverse skin reactions should continue until they have resolved, even if treatment is discontinued or the dose reduced. Once a skin reaction has sufficiently resolved, typically to grade 1 or no rash, treatment should be restarted or the dose increased to the initial dosage, and you can expect this toxicity to remain well managed.

MANAGEMENT OF EGFR-ASSOCIATED RASH

RASH SEVERITY	INTERVENTION
Mild (CTCAE grade 1) Generally localized Minimally symptomatic No impact on ADL No sign of superinfection	Continue EGFR inhibitor at current dose, and monitor for change in severity No treatment[a] **OR** Topical hydrocortisone[b] (1% or 2.5% cream) or clindamycin (1% gel)[a], or both Reassess after 2 weeks If reactions worsen or do not improve, proceed to next step
Moderate (CTCAE grade 2) Generalized Mild symptoms (for example, pruritus, tenderness) Minimal impact on ADL No sign of superinfection	Continue EGFR inhibitor at current dose, and monitor for change in severity Continue treatment of skin reaction Hydrocortisone[b] (2.5% cream) or clindamycin (1% gel) or pimecrolimus(1% cream) + Doxycycline (100 mg twice daily) or minocycline (100 mg twice daily) Reassess after 2 weeks If reactions worsen or do not improve, proceed to next step
Severe (CTCAE grade 3/4) Generalized Severe symptoms (for example, pruritus, tenderness) Potential for superinfection	Reduce EGFR inhibitor dose per label, and monitor for change in severity Continue treatment of skin reaction Hydrocortisone[b] (2.5% cream) or clindamycin (1% gel) or pimecrolimus (1% cream) + Doxycycline (100 mg twice daily) or minocycline (100 mg twice daily) + Methyl-prednisolone dose pack Reassess after 2 weeks If reactions worsen, dose interruption or discontinuation may be necessary

Source: V Hirsch (2011) *Curr Oncol* 18:126–138

Diarrhoea with EGFR inhibitors

Diarrhoea is another toxicity commonly associated with EGFR inhibition. The toxicity profile for the ZETA study with vandetanib showed that diarrhoea was the most common adverse event, affecting 56% of patients and reaching grade 3 or higher in 11% (*JCO* 2011, 30:134–141). Importantly, diarrhoea in patients treated with vandetanib can be associated with colitis.

Vandetanib may also be associated with QT prolongation, so it is very important to check blood electrolytes and ECGs in patients with very profuse diarrhoea, to check there are no imbalances that may potentiate other adverse events of vandetanib.

The first step in management is to investigate other potential causes of a patient's diarrhoea, including: other medications they may be taking, such as laxatives, stool softeners or antibiotics; lifestyle factors, such as excessive dietary fibre or lactose; and infectious causes of diarrhoea.

Diarrhoea associated with EGFR TKIs is usually mild to moderate, and early management is essential to prevent dose reduction or discontinuation of treatment. Management is similar as for diarrhoea associated with chemotherapies. Antimotility agents such as loperamide should be initiated on appearance of mild diarrhoea, and patients should avoid foods that cause symptoms, and eat a simple 'BRAT' diet (bananas, rice, apple sauce and toast). Patients should be advised to drink approximately three litres of liquids a day to minimise the risk of dehydration.

Patients should return to the clinic for further assessment if their diarrhoea persists despite up to 20 mg

loperamide per day. For patients with persisting grade 2 or 3 diarrhoea, interruption of treatment may be considered to allow symptoms to improve. The dose of treatment may also be reduced to control diarrhoea. If diarrhoea fails to resolve after dose reductions or discontinuation, octreotide may be considered in some cases, but it is very rarely needed to manage EGFR TKI diarrhoea, and there is little evidence that supports its use in this situation.

Mucositis with EGFR inhibitors

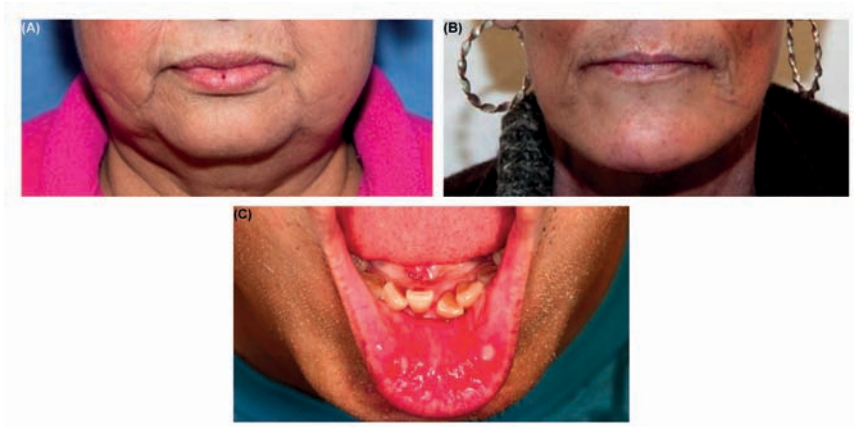
Mucositis is another common side effect with EGFR TKIs. In the LUX-LUNG 3 study with afatinib, 72.1% of patients had mucositis, which was grade 3 or higher in 8.7% of the patients (*JCO* 2013, 31: 3327–34). The figure below shows some examples of mucositis and explains the management of different grades.

Several general measures are very useful for managing mucositis. Before the start of treatment, patients should have an oral hygiene check-up. Advise the patient to brush their teeth and tongue with a soft-bristled brush in addition to flossing and rinsing with normal saline.

Oral mucositis generally starts as a tingling sensation in the mouth, with patients becoming very sensitive to food and beverages, and eventually developing ulcers. Grade 1 mucositis is a minor symptomatic inflammation of the mouth; grade 2 causes some pain but eating and drinking are tolerable; patients with grade 3 mucositis can experience severe pain that prevents them eating or drinking.

If a patient develops mucositis in the mouth, they should rinse their mouth out every two to three hours. Mouthwash or bicarbonate can be useful for grade 1 mucositis. Patients with grade 2 mucositis should apply triamcinolone paste two to three times daily, and mouthwashes that include corticosteroid are very useful for treating mouth ulcers that may develop. If a patient develops grade 3 mucositis you should typically stop EGFR inhibitor treatment for two to four weeks. Oral antibiotics or mouthwashes that combine corticosteroids with antibiotics are very useful. Don't forget to give analgesics, because grade 3 mucositis can be very painful.

MANAGEMENT OF EGFR-ASSOCIATED MUCOSITIS



Mild (grade 1)	Maintain dose level of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). Apply triamcinolone in dental paste 2–3 times daily as needed.
Moderate (grade 2)	Maintain dose level of EGFR TKI. Apply triamcinolone in dental paste 2–3 times daily as needed **AND** oral erythromycin 250–350 mg daily **OR** minocycline 50 mg daily.
Severe (grade 3)	Temporarily discontinue EGFR TKI for 2–4 weeks. Upon improvement to grade 2 or less, reintroduce EGFR TKI at a dose of the physician's discretion. If toxicities do not worsen, escalate the dose. If no improvement, discontinue. Apply clobetasol ointment 2–3 times daily as needed **AND** oral erythromycin 500 mg daily **OR** minocycline 100 mg daily.

Source: B Melosky et al. (2015) *Curr Oncol* 22:123–132

Toxicities associated with VEGFR inhibitors

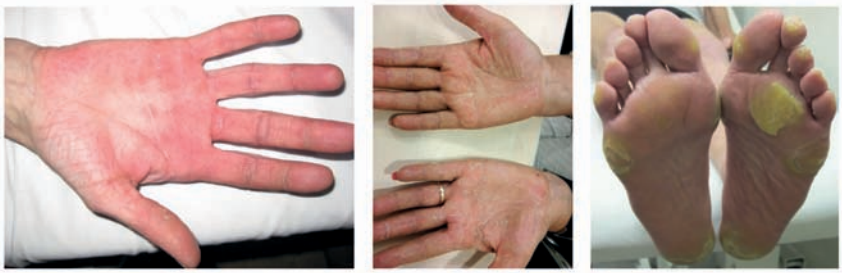
Hand-foot skin reaction (HFSR), hypertension, left ventricular dysfunction and elevated liver enzymes are common toxicities associated with VEGFR inhibitors.

Hand-foot skin reaction

The incidence of HFSR in the CORRECT trial with regorafenib in colorectal cancer was 47%, with grade 3

VEGFR-ASSOCIATED DERMATOLOGICAL TOXICITIES

GRADE 1	GRADE 2	GRADE 3
Minimal skin changes or dermatitis (e.g. erythema, oedema, or hyperkeratosis) without pain	Skin changes (e.g. peeling, blisters, bleeding, oedema, or hyperkeratosis) with pain, limiting instrumental activities of daily living	Skin changes (e.g. peeling, blisters, bleeding, oedema, or hyperkeratosis) with pain, limiting self-care activities of daily living



Source: Adapted from the US NCI's Common Terminology Criteria for Adverse Events (CTCAE) v4.0. Photos provided by Siegfried Segaert and Eric Van Cutsem, and reprinted from B McLellan et al. (2015) *Ann Oncol* doi:10.1093/annonc/mdv244, with permission from Oxford University Press

HFSR in 17% of patients (*Lancet* 2013, 381:303–312). With another VEGFR inhibitor, cabozantinib, the incidence of HFSR was 50% in the MTC study (*JCO* 2013, 31:3639–46). HFSR associated with VEGFR inhibitors and other targeted treatments show some particular features that are different to HFSR associated with traditional cytotoxic chemotherapies.

In HFSR associated with multikinase inhibitors, patients typically complain of dysaesthesia with tingling that develops into burning over a few days. They develop bilateral, painful erythema and also large, intense blisters that evolve eventually into hyperkeratosis. The pain may be completely out of proportion to the clinical appearance of the lesions. Symptoms typically occur at pressure points, such as the palms of the hands or the soles of the feet, particularly the heels and the metatarsal hand areas, and also the elbows.

The figure above shows some examples of dermatological toxicities, with minimal skin changes and mild erythema in the first image and severe hyperkeratosis and erythematous areas associated with pain in grade 3 HFSR in the third image.

HFSR usually occurs early, typically within four weeks of starting regorafenib treatment, and most commonly within the first two weeks. It is not life-threatening, but it can negatively affect a patient's quality of life, so it is important to manage HFSR carefully. Prompt initiation of management can reduce the severity and the duration of HFSR, and close monitoring during the first two cycles of treatment is crucial. I assess patients each week during the first four to six weeks of treatment, and treat promptly if mild symptoms of HFSR appear.

In terms of management, for grade 1 HFSR the skin should be kept well hydrated, but humidity is not helpful. If symptoms reach grade 2, TKI treatment may be stopped in some cases. Hyperkeratosis should be controlled, the skin kept moisturised and discomfort relieved with analgesic. The goals for treating grade 3 HFSR are to reduce symptoms and the impact on the patient's quality of life. Each TKI has specific recommendations for discontinuing treatment and reducing the dose, so it is important to follow these in managing symptoms of HFSR.

Hypertension with VEGFR inhibitors

Hypertension is the most common cardiovascular-related toxicity associated with several VEGFR inhibitors such as axitinib and lenvatinib. In the SELECT trial with lenvatinib it was the most common side effect, affecting 67.8% of patients (*NEJM* 2015, 372:621–30). Typically it occurs early, within three to four weeks of starting treatment.

Before starting TKI therapy, a patient's blood pressure should be controlled for approximately one week. Their blood pressure should be carefully monitored, with weekly measurements in the first cycle of treatment, and then every two to three weeks, or more frequently if required. It is not recommended that treatment is stopped for any grade of hypertension, but in a patient with grade 2 or 3 hypertension that is difficult to control, it can be useful to stop the TKI and get the blood pressure back under control.

Patients who develop stage 1 hypertension or who have >20 mmHg increase in diastolic blood pressure should start hypertensive therapy and you should consider modifying the dose or add a second antihypertensive to achieve recommended blood pressure, following hypertension guidelines.

Left ventricular dysfunction (LVD) with VEGFR inhibitors

Left ventricular dysfunction (LVD) is more common with sunitinib and sorafenib, although it may occur with axitinib. You should consider measuring left ventricular ejection fraction (LVEF) at baseline, but the ideal time for cardiac follow-up is not yet established for these drugs. Ask patients about cardiovascular risk factors that would mandate LVEF assessment before starting treatment.

When symptoms occur, or when LVEF decreases to less than 50% or by more than 10% from baseline, interrupt the treatment or reduce the dose. Good communication and collaboration with a cardiologist is very important in managing these patients. The effect on LVEF is generally reversible on stopping treatment.

Elevated liver enzymes

Elevated aspartate aminotransferase (AST) or alanine transaminase (ALT) is a common side effect with many TKIs. The first step in management is to rule out other causes, such as other drugs or infections. Monitor liver enzymes as clinically indicated throughout treatment, and measure ALT and AST levels before each cycle. Drug interruption or dose adjustments are useful and can generally manage this side effect well.

Pneumonitis associated with ALK inhibitors

Non-infectious pneumonitis is associated with ALK inhibitors. It is not very common but there may be potential issues, making it important to consider. In the phase I trial of ceritinib that led to accelerated approval, pneumonia and pneumonitis were the most frequent adverse drug reaction s that led to discontinuation, affecting 1% or more of patients (*NEJM* 2014, 370:1189–97).

It is difficult to distinguish whether pneumonitis is associated with treatment or due to disease in lung cancer patients, but it is important to be aware of the potential association with ALK inhibitors to guide optimal management.

Drug-induced non-infectious pneumonitis is a diagnosis of exclusion. Patients may have other conditions that may cause dyspnoea and cough. General guidelines on management recommend:

- Rule out other causes for respiratory distress: infections, occupational, recreational or environmental exposures; specific respiratory disorders such as asthma; and systemic diseases.
- Work up: Chest CT scan, bronchofibroscopy to rule out infectious causes, DLCO measurement (if baseline values are available).
- Treatment: stop ALK inhibitor treatment. Treat with corticosteroids and supportive treatment, such as bronchodilators, supplementary oxygen, and mechanical ventilation.
- For cediranib: the recommendation is to permanently discontinue treatment in the event of any grade of pneumonitis.

Haematological toxicities with ABL and JAK inhibitors

Thrombocytopenia, anaemia and neutropenia are typically associated with ABL and JAK inhibitors. Blood count alterations are common with these agents, with 42% of patients having thrombocytopenia and 28% anaemia with bosutinib in a phase I/II study (*Blood* 2014, 123:1309–18).

These toxicities are managed with dose reduction or temporary discontinuation. Specific guidelines in the summary of medicinal product characteristics for ponatinib and bosutinib set out when to reduce the dosage, when to restart and when to discontinue. Some patients need blood transfusions or growth factors, but dose reductions can usually manage these toxicities. ■

TAKE-HOME MESSAGES: PREVENTING AND MANAGING TKI-ASSOCIATED TOXICITIES

- Toxicities with new (and old) TKIs may be predictable, with some class effects such as rash with EGFR inhibitors and hypertension with VEGFR inhibitors.
- Awareness of these toxicities can decrease their seriousness by enabling prevention and prompt management, which can improve patient care and quality of life.
- Maintain good communication with patients, listening to what they tell you and asking about potential side effects.
- The mainstay of management for TKI toxicities is intensive supportive care, dose holding and, if needed, dose reduction.

Living well with advanced breast cancer

MARC BEISHON

Sustaining a good quality of life becomes harder as cancers progress. Advocates are saying their needs have gone unmet for too long, and are working with professionals to define what they need and how best to access it.

Quality of life is important to everyone with an illness, but for those with advanced cancer there is a particular spectrum of needs that affect wellbeing – some of which are more 'unmet' than others.

Some of these relate to healthcare, such as managing the symptoms of the cancer, the side-effects of the treatment, and anxiety and depression. But people with advanced cancer also have other needs, which include effective communications with health professionals, emotional support from family and friends, and practical support to enable them, for instance, to stay working, access insurance, or get help with financial hardship.

Women (and some men) with advanced breast cancer comprise one of the largest groups to face these issues, and they are the focus of the Advanced Breast Cancer consensus conference, now coming up to its third event (ABC3), in Lisbon in November. A group of experts – who include patient advocates – draw up consensus guidelines following the conference, and they recognise that quality of life is fundamental to people with advanced disease, because it is one of the main aims of treatment.

While the population living for many years with metastatic breast cancer is growing, owing to a variety of new drugs, median survival has remained at about two to three years for some time. Around 40% of people with locally advanced (stage 3) disease die within five years.

During much of this time, women are likely to be undergoing various treatments, and there is an "implicit assumption", the ABC guidelines say, that recording of adverse events by clinicians reliably documents patients' side-effects and symptoms. "However," they add, "there is an accumulating body of evidence suggesting that the frequency and severity of many symptoms that impact on an individual patient's quality of life go under-reported, under-recognised, and consequently undertreated."

Since the advent of chemotherapy, research groups have developed various instruments that aim to capture quality of life measures in clinical trials, notably the European Organisation for the Research and Treatment of Cancer (EORTC), which pioneered such tools as far back as 1980.

Tumour-specific scales, such as for breast cancer, have been developed, and there is a growing interest in

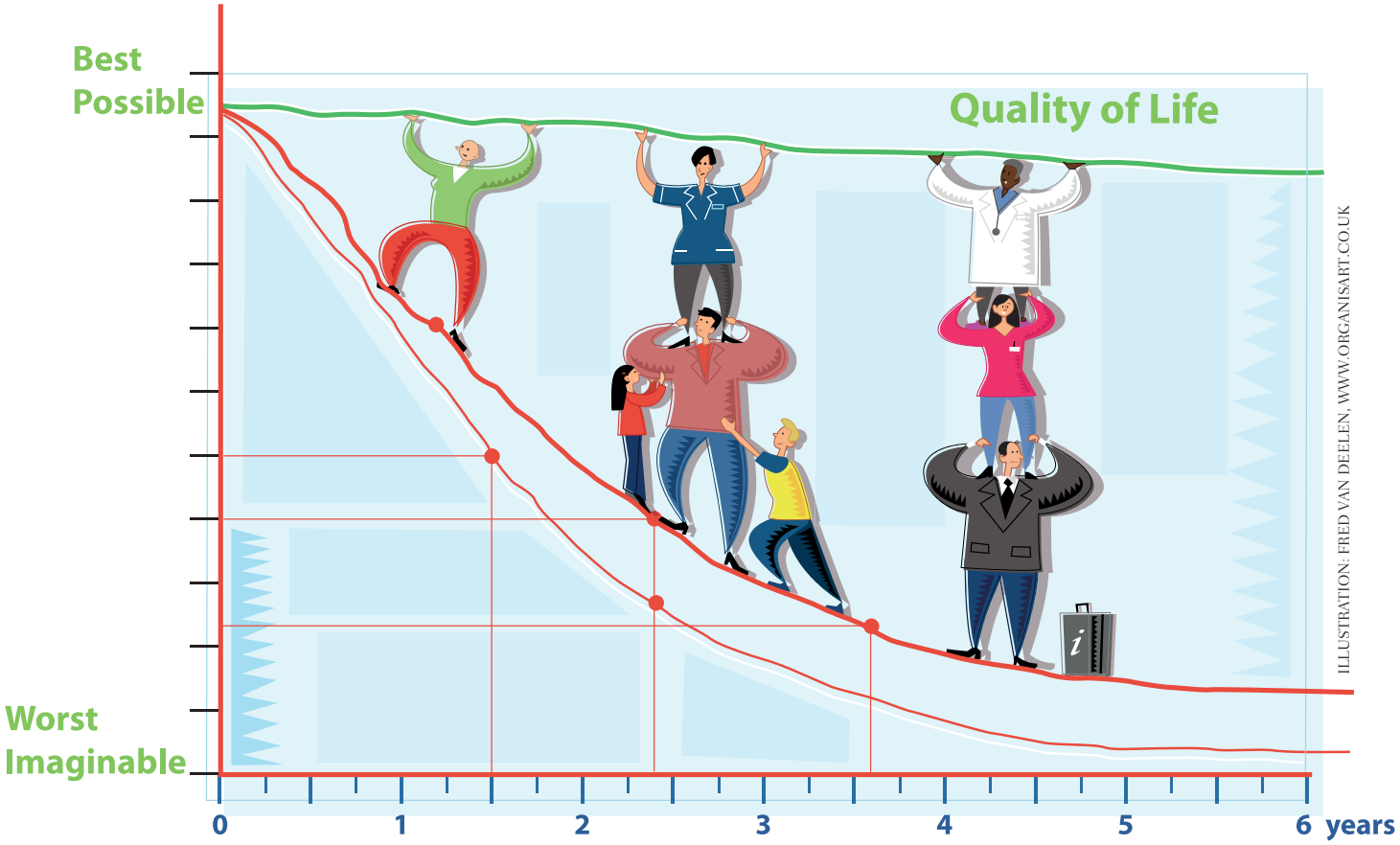


ILLUSTRATION: FRED VAN DEELEN, WWW.ORGANISART.CO.UK

capturing the patient experience outside of clinical trials – mainly using various patient-reported outcomes (PRO) tools.

Musa Mayer, who runs the US-based patient advocacy site AdvancedBC.org, and is a member of the ABC consensus group, points out that much of the emphasis on quality of life has been on the health-related aspects of treatment. The ABC guidelines do also recommend providing comprehensive information, and state that, where possible, specialist cancer nurses (or preferably breast specialists) should be part of the team managing patients with advanced breast cancer, to offer wider support.

But as Mayer notes, it is harder to make more recommendations about other aspects of survivorship for an audience of global health professionals, given wide variations in societies and health systems. The discussion in the guidelines does emphasise, however, that as early as possible a multidisciplinary approach should encompass not only physical, but also functional, social, psychological and spiritual domains; that the disease context and the challenge of uncertainty should be discussed with patients and families; and certain needs should be supported such as social security, job flexibility, rehabilitation, body image (including sexuality), and home and childcare.

"That briefly sums up the extent of

"Care should encompass not only physical, but also functional, social, psychological and spiritual domains"

"Quality of life tools may be too long and complicated to be used in day-to-day clinical practice"

possible unmet needs for advanced breast cancer patients that I have been expanding on in work for the Metastatic Breast Cancer Alliance in the US," says Mayer. "What we have found is that, contrary to expectations, there have been a lot of studies that document many of the unmet needs and ways to solve them, but most of the work has been small scale and qualitative. But there are also a number of patient and advocate surveys, such as those supported by Novartis and Pfizer, that have added much information. To help describe the needs we have grouped quality of life into six categories – they do overlap but are relatively discrete." (See panel opposite.)

Mayer highlights findings in these categories, starting with psychosocial distress, which the evidence suggests is widely prevalent among patients of all backgrounds. "But many patients are not being offered mental health services and this is leading to a lot of unnecessary suffering," she says. "It can become particularly acute as the disease progresses and women are less able to carry out everyday activities that are critical to their wellbeing, but this is often when they are least able to ask for the help they need."

Closely allied is emotional support, which Mayer feels especially strongly about. "My own experience with having breast cancer taught me that women with advanced disease suffer from much stigma and can often be made to feel unwelcome in support groups. Their needs and concerns are typically quite different. Peer support from other patients with advanced cancer is often helpful, as friends may withdraw, and it's typical for emotional support to erode over time as the illness progresses."

Making informed decisions about treatment depends on the quality of information and communication from health professionals. "Treatment choices are individualised and often complex, and because recurrence of breast cancer is rarely discussed by health professionals, many women don't understand the difference between being diagnosed with early breast cancer and recurrent metastatic disease," says Mayer. "After treatment for early breast cancer, it's not unusual to want close surveillance and many unnecessary tests."

Practical issues such as paying for care and access to insurance vary according to national policies. "Financial hardship is clearly one of the biggest issues in the US, but it also disproportionately affects the uninsured, minorities and those living in rural areas," says Mayer. Issues such as getting time off work for treatment, arranging childcare or losing a job can arise anywhere.

And physical symptoms of having advanced breast cancer represent just one of the six dimensions. Mayer notes that people are often hesitant to 'bother' their oncologists about symptoms, wishing not to be seen as 'complainers'. There can also be ambivalence about palliative care or more aggressive treatments during the disease course.

In the clinic

For many, quality of life will revolve around the cancer clinic, but what practically can be achieved currently at hospitals? Galina Velikova, professor of psychosocial and medical oncology at the Leeds Institute of Cancer and Pathology in the UK, has a long-standing interest in quality of life issues, having been concerned in the earlier days of chemotherapy about whether toxic drugs were actually benefiting patients. She has chaired the EORTC's Quality of Life Group, and is also now President of the International Society of Quality of Life Research.

"Quality of life instruments, such as the EORTC's, capture symptoms and side-effects, physical function and some psychosocial aspects and so are good starting points," she says. "But they have been developed to assess drugs in clinical trials, and a big problem is that they may be too long and complicated to use in day-to-day clinical practice. There is also no agreement on which ones to use, and they can be out of date. For example, we are doing an update of the EORTC breast cancer module now because, as it was one of the first cancer-specific modules we did, it doesn't take account of new systemic therapies and new surgical and radiotherapeutic techniques."

Her own work has included designing and validating self-report questionnaires for patients that can be used by clinicians to monitor people during drug therapy, and are most useful in helping to assess side-effects, which when controlled can

allow people to function better (see www.pogweb.org). In breast cancer, most of this work is on chemotherapies delivered in the clinic, and Velikova says she's hoping to get funding to do similar research on oral targeted drugs, where monitoring is harder to do as patients take them at home, away from hospital staff.

"It may be that this approach will guide us to use drugs with fewer side-effects," she says, adding that an aim is also to integrate self-reports into electronic patient records to increase the potential for personalised treatment and research. This is difficult to achieve on a wider scale in large hospitals or health care organisations, and Velikova says that typically only 'local champions' will be able to swing support from hospital administrations to make this a standard for more integration.

Capturing and acting on psychological aspects is yet more difficult. "Oncologists and nurses are not good at diagnosing emotional distress and anxiety," says Velikova, and in any case many patients don't always want help and prefer to focus on their treatment, she adds. "We have done a trial where we screened patients for depression and anxiety and provided this information to clinicians. Although clinicians discussed emotional issues more frequently with those patients, the patients didn't accept more referrals to psycho-oncology or other professional help. This seems to be true for those with mild and moderate symptoms, but there is no doubt we need to identify and refer those with severe depression."

Mayer comments that there is stigma associated with mental health diagnoses and seeking help. "In the US this is a significant barrier. I agree though that medical professionals often don't recognise treatable anxiety and depression and mistakenly think it 'goes with the territory' of advanced cancer."

Velikova argues that cancer centre professionals, and in particular nurses, should be trained in communications skills for giving information and listening to concerns, and also to detect possible emotional distress.

This has been put forward, for example, in the UK guidelines for supportive and palliative care. "Clinical nurse specialists can engage in counselling and cognitive problem solving for low-level distress, and related to this we have had a programme in the UK on advanced communications skills funded by the National Cancer Action Team, but funding has tailed off now, which is a pity."

Ideally, cancer centres should also have nurses who specialise in metastatic cancer, given that there is such a wide range of tumour types, treatments and disease trajectories. "Breast cancer can vary from aggressive in

THE SIX DIMENSIONS OF QUALITY OF LIFE

Six quality of life dimensions are set out in a paper on 'Changing the Landscape for People Living with Metastatic Breast Cancer', published by the Metastatic Alliance in the US, which has carried out a comprehensive distillation of the evidence:

- **Addressing psychosocial distress** – it is estimated that a third of patients suffer from mood disorders such as anxiety and major depression; the theme of loss is pervasive, such as loss of attractiveness and roles in family life; and many lack access to mental health services. But much can be done to equip people with adjustment and coping mechanisms, and to gain control over feelings of loss. Studies also show that better emotional function is linked to fewer physical symptoms.
- **Emotional support** – support from family, friends, advocacy groups and healthcare professionals can be crucial, as having advanced disease can lead to social withdrawal and stigma. While nearly all patients value emotional support, its desired form can vary greatly among individuals.
- **Information** – access to high-quality information is a need for most patients, and seeking information is part of gaining control, but many also say information is hard to find and can be confusing. Different types and sources of information are needed throughout the disease course.
- **Communication and decision-making** – this is a complex area as patients vary in the degree to which they want to take part in decision making, but many in any case do not receive guidance. Clear lines of communication at the end of life, while difficult for patients, families and healthcare providers, allows for better palliative care, and ensures that the patient's wishes will be respected.
- **Relief of physical symptoms** – fatigue is by far the most common symptom reported by patients and is often difficult to treat. Chronic pain is another common symptom, as are sleep problems. Communication difficulties about symptoms exist on both sides of the patient–professional relationship.
- **Practical issues** – a majority of people with metastatic breast cancer are in the workforce at diagnosis, according to the Alliance's sources, but within the first year about a half have quit or lost their jobs. Apart from financial hardship and navigating welfare systems, problems include managing the home, childcare, and transport.

"When we measure something it's helpful to have a purpose, but often we don't have answers to hand"

young women to indolent in older women, so there is a big need to provide the right care for each person," says Velikova. "But even in our centre, which is quite large, we have only had one metastatic nurse specialist for about a year and a half now, and that's only been possible through external funding from a charity."

Looking at wider quality of life issues poses other problems, says Velikova. "When we measure something, it's helpful to have a purpose – something we can do about it. But often we don't have answers to hand. Good examples are sexual issues and body image in women with breast cancer – we just don't have specialist services we can send them to. This is very different from factors where we have professionals to help, such as identifying and managing pain."

This doesn't mean that measuring wider quality of life issues isn't important, at least to gauge the size of needs. "We have performed a large study on people living with advanced cancer [breast, ovarian, prostate, renal and colorectal]" says Velikova. "It's a growing population in advanced breast cancer, because we have older patients living much longer with hormone-positive disease, and also young women with HER2-positive cancer, who are often treated with many lines of chemotherapy plus the targeted drugs. These patients know they are not being cured and are 'sitting on a time bomb', and they encounter new problems such as not being able to go on holiday because they can't get insurance. Their psychological needs are not so much depression, but living with uncertainty and the fear of recurrence."

Bringing this group and their needs to the attention of society is an important first step. But one major obstacle to providing better services for, and awareness of, women with advanced disease is simply that, in most countries, no one knows how many there are. Cancer registries tend to record the stage of cancer only at initial diagnosis, which in breast cancer in developed countries, is much more likely to be early-stage disease, so the many people who suffer from advanced metastatic disease are lost from those population statistics.

There has been a pilot in England to register metastatic breast cancer, but there have been no updates on the project lately. "Even with ten years of electronic records at Leeds we don't have a good idea of metastatic disease numbers here," comments Velikova.

So there is a broad range of unmet needs in advanced breast cancer, and one big challenge is that there is no one place where all can be met. Even within the acute healthcare setting there is much room for improvement in personalising both treatment and communications.

Healthcare systems need to do much more to identify how many people are living with chronic cancer and assess all their needs. These will include access to wider mental health services, community support (including advocacy groups, face to face and online) and specialist services. Changes are also needed within society at large, to better accommodate people living with cancer, to eliminate stigma and reduce the obstacles they face in their everyday life.

As Mayer concludes, none of these is insurmountable, as we already know from good practice and projects around the world. It is the aim of the advocates at ABC to give patient groups the evidence and the support to plug the gaps in a sustainable way for people living with advanced breast cancer, which could well help those with other types of advanced cancer too. ■

MAPPING THE POPULATION AND THEIR NEEDS

Apart from mainly small-scale research studies on quality of life, in recent years there have been a number of surveys that have done much to raise awareness of advanced breast cancer. They include the BRIDGE survey in 2009, a global survey conducted by Pfizer on 950 women in nine countries, and Count Us, Know Us, Join Us, and Here & Now, both led by Novartis, with Here & Now being a pan-European initiative.

Both Novartis and Pfizer will be releasing more research at the ABC conference. Novartis will be announcing the next stage in Here & Now, and a call to action. Pfizer is completing a major report and survey of patients, advocacy groups and cancer centres in a number of countries. *Cancer World* will have the highlights of these in our report on ABC3.

newsround

Selected reports edited by Janet Fricker

Higher quality colonoscopies reduce cancer deaths without higher costs

JAMA

Higher rates of detection of precancerous adenoma were associated with lower lifetime risks of colorectal cancer and colorectal cancer mortality and did not result in greater overall healthcare costs, a Dutch microsimulation model study has found.

Colonoscopy reduces colorectal cancer mortality through detection and treatment of precursor adenomatous or early cancerous lesions. However, quality, as measured by adenoma detection rates, varies widely among physicians. While studies suggest that higher adenoma detection rates are associated with better disease detection and better management, little is known about consequences for costs and other benefits of screening programmes.

Reinier Meester and colleagues, from Erasmus University Medical Centre, Rotterdam, carried out microsimulation modelling to estimate the lifetime benefits, complications and costs of an initial colonoscopy screening programme at different levels of adenoma detection. The team used data from the Kaiser Permanente Northern California healthcare system on variations in adenoma detection rates and cancer for 57,588 patients examined by 136 gastroenterologists between January 1998 and December 2010.

For the study, no screening was compared with colonoscopy screening according to adenoma detection rate quintiles (divided into five groups). The mean adenoma detection rates were 15.32% for quintile 1, 21.27% for quintile 2, 25.61% for quintile 3, 30.89% for quintile 4 and 38.66% for quintile 5.

The model estimated that, among unscreened patients, lifetime colorectal cancer risk was 34.2 cases per 1,000 patients, compared to 26.6 per 1,000 for those in quintile 1, 21.6 per 1,000 for those in quintile 2, 19.0 per 1,000 for quintile 3, 15.6 per 1,000 for quintile 4, and 12.5 per 1,000 for quintile 5. The simulated incidence of death from colorectal cancer was 13.4 per 1,000 patients for unscreened patients compared to 5.7 per 1,000 for those in quintile 1, 4.5 per 1,000 for those in quintile 2, 3.7 per 1,000 for those in quintile 3, 3.0 per 1,000 for quintile 4 and 2.3 per 1,000 for quintile 5. The model estimated that lifetime incidence and mortality risks were 11%–13% lower on average for every five-point higher adenoma detection rates, which translates to overall differences of 53–60% between the lowest and highest quintiles. Estimated net screening costs were on average 3.2% lower for every five-point increase in adenoma detection rates, and the risk of complications was on average 9.8% higher for every five-point increase in adenoma detection rates.

"Our results suggest that higher adenoma detection rates may be associated with up to 50%–60% lower lifetime colorectal cancer incidence and mortality without higher net screening costs, despite a higher number of colonoscopies and polypectomy-associated complications," write the authors.

Future research, they add, is needed to assess why adenoma detection rates vary and whether increasing adenoma detection would be associated with improved patient outcomes.

■ R Meester, C Doubeni, I Lansdorp-Vogelaar et al. Variation in adenoma detection rate and the lifetime benefits and cost of colorectal cancer screening. A microsimulation model. *JAMA* 16 June 2015, 313:2349–58

Very low breast density predicts worse survival

European Radiology

Very low mammographic breast density (MBD) at the time of breast cancer diagnosis is associated with higher tumour grade and predicts poorer disease-free and overall survival, a Finnish study has found.

MBD refers to the appearance of breast tissue on mammograms, reflecting variations in breast tissue composition and x-ray attenuation characteristics. Unlike other breast cancer risk factors, MBD – which is influenced by genetic factors – can change over time. It decreases with age and is further reduced by multiparity and menopause. While it is well recognised that MBD in the upper quartile is associated with a four- to six-fold higher risk for developing breast cancer than MBD in the lower quartile, less is known about its possible prognostic importance.

Since high MBD is such a strong risk factor, it could be hypothesised that, in patients with breast cancer, higher densities would yield a worse prognosis. In the current study Amro Masarwah and colleagues, from Kuopio University Hospital, Finland, set out to examine the prognostic value of MBD and other mammographic features in 270 patients, who had a median age of 58 years, with previously diagnosed invasive breast cancer. MBD was classified by consensus among five trained radiologists according to density, with very low density (VLD) <10%; low density (LOD) <25% and mixed density (MID) >25%.

Results at a mean follow-up of 6.4 years showed that disease-free survival was 74.7% (118/158) for patients with LOD versus 84.8% (95/112)for patients with MID (*P*=0.048), and that overall survival was 75.3% for patients with LOD versus 90.2% for patients with MID (*P*=0.003). In Cox regression analysis, in comparison to the other groups VLD proved to be an independent feature predicting poor prognosis (HR=3.275; *P*<0.001) that was second in importance only to tumour size (HR=3.455; 95% CI 1.833–6.511; *P*<0.001). Percentile MBD categories displayed a significant inverse relationship with tumour grade (*P*=0.019), but had no relation to HER2 status, or oestrogen or progesterone receptor status.

"Breast density is a readily available, cheap and easy-to-interpret form of information and, according to our analysis, proved to be an independent and clinically important prognostic feature. The ability to predict the course and outcome of the disease beforehand by analysing certain features on a mammogram is a desirable and useful tool for clinicians," write the authors.

In future breast cancer studies, they add, proper categorisation of breast tissue density is important. "Performing a more detailed radiological subdivision amongst the low density group should be advocated, as only the patients with very low densities showed significant associations with poor survival," write the authors. Studies are needed to clarify hormonal, biological and genetic interconnections between breast density and breast cancer aggressiveness.

■ A Masarwah, P Auvinen, M Sudah et al. Very low mammographic breast density predicts poorer outcome in patients with invasive breast cancer. *Eur Radiol* July 2015, 25: 1875–82

Biomarkers identified for screening pancreatic cancer

Clinical Cancer Research

A three-protein biomarker panel screening test undertaken in urine can be used to detect patients with early-stage pancreatic cancer, report UK researchers.

Despite progress in understanding pancreatic ductal adenocarcinoma (PDAC) at the molecular level, no significant improvements in diagnosis and therapy have been made in the last 30 years. Currently 80% of patients with PDAC present with locally invasive and/or metastatic disease, leaving only 20% eligible for potentially curative surgery. Timely detection of PDAC has been hampered by lack of specific clinical symptoms in the early stage of disease, insufficient sensitivity of current imaging modalities, and lack of accurate body fluid-based biomarkers for early stage disease.

In the current study Tatjana Crnogorac-Jurcevic and colleagues, from Queen Mary University, London, looked to develop a diagnostic test in urine specimens. Urine, the investigators reasoned, offers advantages over blood since it provides an 'inert' and stable matrix for analysis and can be repeatedly and noninvasively sampled in sufficient volumes.

In the discovery phase the team explored levels of 1,500 proteins in urine specimens from six patients with PDAC, six patients with chronic pancreatitis (CP) and six healthy controls. Using GELC/MS/MS assays they found that only 481 of the proteins were common to males and females, and that three of these proteins – LYVE-1, REG1A and TFF1 – were higher in PDAC patients.

For the validation phase, 192 urine samples from PDAC patients, 92 from chronic pancreatitis patients and 87 from healthy subjects were assayed.

When comparing PDAC specimens with healthy urine specimens, the resulting areas under the receiver-operating characteristic curves (which plot true-positives against false-positives, providing information on detection accuracy) were 0.89 (95%CI 0.84–0.94) in the training dataset and 0.92 (95%CI 0.86–0.98) in the validation dataset. When comparing PDAC stage I–II (*n*=71) with healthy urine specimens, the panel achieved areas under the curves of 0.90 (95%CI 0.84–0.96) in the training dataset and 0.93 (95%CI 0.84–1.00) in the validation dataset. Furthermore, an exploratory analysis suggested accuracy was increased when the panel was combined with the CA19.9 protein for patients with PDAC, but not those with stage I-IIA PDAC.

"Being completely non-invasive and inexpensive, this urine screening test could, upon further validation, and when coupled with timely surgical intervention, lead to a much improved outcome in patients with high risk of developing PDAC," write the authors.

The healthy cancer controls, they add, were on average younger than cancer patients, making it important for further validation studies to use older controls.

The improved accuracy with CA19.9, say the authors, may be important in light of recent findings that serum CA19.9 is upregulated for up to two years before PDAC diagnosis.

The priority cohort for screening strategies, they suggest, should include families with a high incidence of pancreatic cancer (at least two affected first-degree relatives) and individuals with hereditary conditions, such as intestinal polyposis syndrome Peutz-Jeghers.

■ T Radon, N Massat, R Jones et al. Identification of a three-biomarker panel in urine for early detection of pancreatic adenocarcinoma. *Clin Cancer Res* 1 August 2015, 21:3512–21

Assisted reproductive technology has no influence on breast cancer outcomes

European Journal of Cancer

Pregnancy using assisted reproductive technology (ART) in women with a history of breast cancer is feasible and does not appear detrimental to cancer outcomes, a European multicentre retrospective study has found.

With around 65–70% of young breast cancer patients alive and free of distant relapse 10 years after diagnosis, there is a need to explore the feasibility and safety of ART in breast cancer survivors whose fertility may have been impaired by treatment.

In the current study Oranite Goldrat, from Erasme Hospital in Brussels, Belgium, and colleagues from Brussels, Milan, Macerata, Barcelona and Denmark, for the first time set out to evaluate the effect of using assisted reproductive technology on rates of recurrence and death in patients who were previously treated for breast cancer and subsequently became pregnant.

Women aged 18 to 45 years, who were diagnosed with primary non-metastatic breast cancer between 2000 and 2009 and who subsequently became pregnant, were eligible for the study. The cohort was divided into two groups according to whether pregnancies occurred spontaneously (Spontaneous Group) or after using assisted reproductive technology (ART Group). Data were collected on clinico-pathological characteristics, breast cancer treatment (date of diagnosis, histological type, histological grade, tumour size, nodal status, endocrine receptor status, HER2 status, type of breast surgery, chemo- and endocrine therapies), fertility treatments (ovulation induction, ovarian stimulation for IVF and oocyte donation) and pregnancy-related information (age at conception, number of pregnancies, and pregnancy outcome).

Results showed that altogether 173 women were followed up in the Spontaneous Group (247 pregnancies) and 25 women in the ART group (34 pregnancies). No significant differences in breast cancer outcomes were observed between the two groups for local recurrence, distant recurrence and contralateral breast cancer (P=0.54 for all). Patients in the spontaneous pregnancy group were younger (mean age: 31.2 vs 33.7 years, P=0.009) and had a higher frequency of histological grade 3 tumours (59.6% vs 36%, P=0.033). On the other hand, women in the ART group had more node-negative, oestrogen receptor- (ER)-positive tumours and shorter durations of endocrine therapy, although these differences did not reach statistical significance.

"Our results indicate lack of a detrimental effect of attaining pregnancy via ART on the risk of recurrence in women with history of breast cancer. While the number of patients included in the study is relatively small, warranting further confirmation, we believe this study would provide physicians with important guidance when counselling their patients in the daily practice," write the authors.

Interestingly, they add, women undergoing ART had more favourable prognostic parameters, suggesting physicians were selective in offering ART to patients with a relatively good prognosis. "This underscores the uncertainty and fear of the safety of ART in women with history of breast cancer," write the authors.

The trend for earlier discontinuation of endocrine therapy among ART patients, they suggest, is due to higher age, leaving women with no choice but to discontinue treatment early.

■ O Goldrat, N Kroman, F Peccatori et al. Pregnancy following breast cancer using assisted reproduction and its effect on long-term outcome. *Eur J Cancer* August 2015, 51:1490–96

Anxiety and health literacy are drivers for salvage androgen deprivation therapy

Annals of Oncology

Among men with asymptomatic prostate-specific antigen (PSA) recurrence after radiotherapy for prostate cancer, use of salvage androgen deprivation therapy was nearly twice as high among men with high levels of anxiety about their PSA or poor health literacy, a US multicentre prospective registry has found.

Although androgen deprivation therapy is part of the standard approach for the initial management of metastatic prostate cancer, no survival benefits have been shown from early use of salvage androgen deprivation therapy for men with PSA-only recurrence after radiotherapy (who may not go on to develop overtly metastatic disease for years).

In the study, Paul Nguyen and colleagues, from Dana Farber Cancer Institute and Brigham and Women's Hospital, used the prospective Comprehensive, Observational, Multicenter, Prostate Adenocarcinoma Registry (COMPARE) to determine whether PSA anxiety or health literacy are associated with unproven use of early salvage androgen deprivation therapy as initial management for PSA recurrence following radiotherapy.

Between February 2004 and March 2007, the COMPARE registry enrolled 1,120 men across 150 geographically diverse sites with biochemical (PSA) recurrence after primary therapy for localised prostate cancer. A total of 375 participants met the inclusion criteria of having received radiotherapy (external beam radiotherapy or brachytherapy) but not radical prostatectomy as initial treatment, and having complete information on PSA anxiety (assessed using three questions from the Memorial Anxiety Scale for Prostate Cancer) and health literacy (based on the Rapid Estimation of Literacy of Medicine [REALM-SF]).

For REALM-SF, patients were asked to pronounce seven medical words out loud (menopause, exercise, rectal, behaviour, antibiotics, jaundice, and anaemia), to give literacy levels higher than ninth grade (all words pronounced correctly) and lower than ninth grade (fewer than seven words pronounced correctly).

Results showed 68 men (18.1%) received salvage androgen deprivation therapy as initial management for PSA recurrence. For men with high PSA anxiety, 28.8% received salvage androgen deprivation therapy compared to 13.1% who did not have high anxiety (univariable OR=2.15, 95%CI 1.16–4.00, *P*=0.0015; multivariable OR 2.36; 95%CI 1.21–4.62; *P*=0.012). For men who had higher level of health literacy, 15.2% underwent salvage androgen deprivation therapy compared to 26.3% with lower levels of health literacy (univariable OR=0.50; 95%CI 0.29–0.88, *P*=0.016; multivariable OR=0.58; 95%CI 0.32–1.05; *P*=0.07).

"These findings suggest that patient-level concern or understanding are significant drivers… of receipt of salvage ADT [androgen deprivation therapy] at biochemical recurrence after radiotherapy and men with high PSA anxiety or low health literacy may be more likely to push for or accept treatment," write the authors.

Given that early salvage androgen deprivation therapy is costly, worsens quality of life, and has not been shown to improve survival, write the authors, quality improvement strategies are needed to help these individuals. "Oncologists should ensure that anxious and less health literate patients are adequately counselled about the benefits and risks of salvage ADT before they decide to pursue therapy. A concerted effort to ensure that patients' worries, anxieties, and uncertainties are addressed could prevent many patients from undergoing early initiation of salvage ADT."

■ B Mahal, M Chen, C Bennett et al. High PSA anxiety and low health literacy skills: drivers of early use of salvage ADT among men with biochemically recurrent prostate cancer after radiotherapy. *Annal Oncol* July 2015, 26:1390–95

Educational attainment influences suspicion of cancer

European Journal of Cancer

Levels of cancer suspicion following 'warning symptoms' were low overall, and even lower among less educated respondents, a community sample questionnaire has found.

Studies where cancer patients report retrospectively on the process of symptom appraisal have suggested that failing to recognise symptoms that are due to cancer is an important factor determining delays in presentation. Prolonged intervals from symptom onset to seeking help may increase the risk of being diagnosed at a late stage. It has also been found that people with lower socioeconomic status are more likely to be diagnosed with later-stage disease for several cancer sites.

For the current study, Katriina Whitaker and colleagues, from the University of Surrey, in Guildford, UK, emailed two separate primary-care-based symptom surveys (using the same questions) to 9,771 adults aged over 50 years, with no cancer diagnosis, to test the hypothesis that people with less education are less likely to suspect cancer when they experience a cancer 'warning sign'.

Respondents were asked whether they had experienced any of 10 cancer 'warning signs', taken from the Cancer Research UK's website, in the past three months. The warning signs were: persistent cough or hoarseness, persistent change in bowel habits, persistent unexplained pain, persistent change in bladder habits, change in appearance of a mole, unexplained lump, sore that does not heal, unexplained weight loss, persistent difficulty swallowing and unexplained bleeding. All had yes/no responses, and for each symptom respondents experienced they were asked: "What do you think caused it?" Surveys also included questions about marital status, employment, ethnicity, and education (university versus below university).

Results showed that nearly half the respondents (1,790/3,756) had experienced a 'warning sign', but only 3.5% (63/1,790) of these mentioned cancer as a possible cause. The highest number of cancer suspicions was for change in the appearance of a mole (10.7%), while the lowest number was for a change in bladder habits (0.7%).

Lower education level was associated with lower likelihood of cancer suspicion: 2.6% of respondents with school-only education versus 7.3% with university education suspected cancer as a possible cause. In multivariable analysis, low educational level was the only demographic variable independently associated with lower cancer suspicion (OR=0.34). There were no significant associations with sex, age, marital status, employment or ethnicity.

"Our finding that people in general have low cancer suspicion when they experience 'warning signs', and that this is even lower in those more likely to be diagnosed at a later stage is important. People may need to be encouraged to lower their cancer suspicion 'threshold' through earlier diagnosis interventions, both at the public health and GP level," write the authors.

One issue for consideration, they add, is the tension between encouraging people to think seriously about symptoms that could give an early warning of cancer and creating fear or hypochondria. A possible solution, they suggest, is to develop educational information that associates symptoms with potential illness rather than cancer.

■ K Whitaker, K Winstanley, U Macleod et al. Low cancer suspicion following experience of a cancer 'warning sign'. *Eur J Cancer* (in press) doi.org/10.1016/j.ejca.2015.07.014


Eat me

Dangerous healers

BERNHARD ALBRECHT

It's not uncommon for people diagnosed with cancer to explore how alternative practitioners might help. Some can, or at least do no harm. But the chances of running into a charlatan whose advice could be fatal are shockingly high, as this undercover investigation, first published in the German magazine *Stern*, demonstrates.

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

The spirit healer had inherited her 'gift' from her father. She now wants to use it to help us make a potentially life-or-death decision: whether or not to have surgery for breast cancer. We have travelled more than 1000 kilometres from Hamburg to this Swiss village, with a population of around 3000, for advice. The practice, on the first floor of a 1960's house, has a sombre feel – grey carpeting, black leather chairs in the waiting room, and certificates on the walls.

She had described over the phone how she makes her diagnoses: "I place my hands on the chest and absorb the tumour's energy. I then sense its activity, whether it is spreading rapidly or slowly." Today, she faces a different challenge. Katja, acting as my wife, does not really have breast cancer. Her diagnostic records – a mammogram and a histologic examination – have been taken from another patient.

The Swiss healer is the last on our list. We've been to 19 other practitioners of alternative medicine before her, and have now reached the end of a three-week journey through the world of miracle healers. We have consulted 10 naturopaths and 10 doctors practising alternative medicine.

I had selected the healers in consultation with two academics, both authors of textbooks on alternative medicine, and familiar with the scene: Jutta Hübner, from the German Cancer Society, and Karsten Münstedt, consultant oncologist at the University Hospital of Giessen. All our healers claim to specialise in cancer care. We found them on Google, using the sort of search terms that might occur to a distressed woman when first diagnosed with breast cancer, such as "alternative treatments for breast cancer" or "alternative medicine for cancer". Seventeen German doctors and German-registered naturopaths came up with the most hits on Google, and a further three were recommended

For every woman being seduced to undergo alternative medical treatment, there is a seducer

by one or other of them, including the Swiss spirit healer, who "deliberately" didn't have her own website.

One in four Germans believe in the powers of miracle and spirit healers, and a good 40% believe in astrology. Cancer patients are vulnerable to unsubstantiated promises of a cure, as indicated by the Amazon bestseller list. Of the 20 bestsellers in the category 'cancer', the vast majority centre on conspiracy theories or promote cancer diets as cures.

I share many of the misgivings about cancer treatment in clinical practice; in particular, the increasing number of very expensive therapies of questionable value being put on the market by pharmaceutical companies. Moreover, doctors do often fail to fully appreciate the level of patients' anxiety, and they can get things wrong. Yet there's no denying the great progress oncology has made in the treatment of certain cancers in recent decades. At an early stage, breast cancer can be cured.

Whether to go for surgery, yes or no, is usually the most urgent question people face on being diagnosed with cancer. The late founder of Apple, Steve Jobs, decided against when he was diagnosed with pancreatic cancer. He underwent alternative treatment for nine months, without success. In his biography, he called it a mistake.

There are no figures on how many women refuse any form of conventional medicine. I have, however, talked to self-help organisations and many gynaecologists and oncologists. They have all encountered women who had opted for alternative treatment, and only sought surgery when their breast cancer had become a festering sore. "We see one every month," says Marion Kiechle, head of the gynaecology department at the Rechts der Isar Hospital in Munich. What promises are being made to these women behind closed doors? For every woman being seduced to undergo alternative medical treatment, there is a seducer.

Three years ago, I wrote the story of one of these seduced women. For Renate Molofwa, who spent four years in the jungle of alternative medicine, the surgery came too late; she died in January 2013. If she had gone for surgery when first diagnosed, she would probably now be free of cancer. She wanted that article to send out the message: "Don't be as gullible as me!" I now want to find out what the chances are of running into a delusional charlatan when searching for a gentle alternative to conventional treatments.

Our roles as a pair are clearly defined. Actress Katja is looking for an answer to an important question: "On the basis of these diagnostic findings, should I opt for surgery or not? She should convey uncertainty, to induce the consultant to respond with advice that could potentially be life-changing. What they say might, after all, determine what a distressed patient ultimately decides to do. I don't tell them that I am a doctor, but allow myself to be guided by their advice. Occasionally I ask stupid questions, make out I mishear things or repeat the same question several times, as this exercise needs to be done properly: in court cases, charlatans often claim to have been misunderstood. We always ask the same questions: Can our candidates read the diagnostic findings? How do they rate conventional medicine and surgery? What treatments do they suggest and how much do they cost?

Did they understand the pathology report?

The Swiss spirit healer takes her time reading through the pathology report. The silence is broken only by the chimes of a distant church clock. Five minutes pass. The task is relatively straightforward. There are a number of key bits of information, which are easy to find, provided you read all three pages. These are: "G3", "focal invasion… 4 mm", and "oestrogen receptor: 80%". They indicate that the tumour is growing very fast, but is still very small. This means the prospects for a cure are excellent. Assessing the prognosis for different types of breast cancer is based on experience that has accumulated across the world over several decades.

Our pathology report indicates that the patient has a 90% chance of remaining free from cancer for 10 years following surgery. This increases to more than 95% if she goes for all the conventional treatment options open to her. It doesn't even require the dreaded chemotherapy, just hormone therapy and intraoperative radiotherapy – a procedure that has fewer side effects

Undercover investigation. The writer of the article, Bernhard Albrecht, sits with Katja, the actress playing the role of a woman diagnosed with early breast cancer, waiting for a consultation

MARCUS VOGEL

than traditional radiotherapy, which is spread over a wider area.

Nobody would expect healers or GPs to provide such detailed information on a breast cancer, but anyone who takes responsibility for advising for or against surgery must read the pathology reports carefully – and understand them.

The people we consulted had taken this heavy responsibility on themselves. Only one admitted he lacked the necessary expertise. "I can only advise you on what other options are open to you." Five of the 20 healers avoided giving an answer, despite being asked repeatedly, or they were not interested in reading the findings. A particularly shocking discovery was that, among our 20 practitioners of alternative medicine, more doctors than naturopaths failed to assess the condition correctly. Five of the 10 doctors assessed the cancer as less of a threat than it was. Some probably just didn't read the pathology report to the end, and so missed key details, while others didn't understand the terminology, such as "G3", which refers to a particular set of cancer cell characteristics, and indicates that the cancer is aggressive and fast-growing. The naturopaths came off better; only one of the six who dared make an assessment was wide of the mark. The other five misinterpreted some

Among our 20 alternative practitioners, more doctors than naturopaths failed to assess the condition correctly

Many of the alternative practitioners we talked to told us of patients with terminal cancer whom they had cured

key terms, but came to the correct conclusion, namely that the tumour was dangerous.

This is particularly disturbing, because most patients will initially consult not only naturopaths but also medical doctors, so the consequence of any misjudgement on the part of a naturopath could be less serious. The five doctors who failed this part of the test, by contrast, offered the full package, saying that they would assess the cancer using a conventional medicine approach, and then plan their alternative treatment accordingly.

This finding is reflected in the experience of breast cancer patient Renate, in her summary of her own four-year odyssey: "I was twice close to death and on both occasions I trusted doctors too much." The first one failed to detect life-threatening anaemia. One day, she showed him her breast, which he had never wanted to see before. She opened her bra, took off the bandage and blood spurted out in his direction. When she saw his horror, she fled. The second doctor failed to notice that the metastasis in her pleura had secreted litres of fluid that was pressing on her lungs. She complained that she could hardly breathe, but he continued to prescribe herbs, ointments and coffee enemas.

The Swiss spirit healer looked up from the papers after five minutes and talked intensely to Katja. Based on a detailed analysis of the diagnostic reports, there was only one thing she could advise: "Go and have surgery! I don't want to see you die young! Your children still need you!" She then talked about other patients who had missed this opportunity. "Only surgery can give you an 80% to 90% chance – without risk." She then began to talk about Katja's family history. Katja had told her that her mother and one of her aunts had developed breast cancer. The healer advised her to have a genetic test and explained that high-risk genes meant she should consider having both breasts removed.

We hadn't been expecting that! Only a few alternative medicine practitioners had spoken up so vehemently for conventional medicine. A shocking 12 of the 20 candidates we'd consulted – both doctors and naturopaths – had seen no need for surgery. They split into two camps: six hardliners who considered their methods better than, or even incompatible with, conventional medicine; and six who expressed themselves in rather overblown language, like this registered doctor: "There are two fundamentally different approaches. Both paths have been trodden, and both have without doubt met with success!" Katja then asked whether this doctor had treated women who had not undergone surgery. "Every day. We have loads of them," she replied emphatically. "And the breast cancer disappears, the body fights it by itself?" Katja asked. "Yes, that's the goal," the doctor confirmed.

Who advised us to go to hospital?

The Medical Director of a naturopathy clinic, who advised us on a telephone hotline at a rate of €1.98 a minute, was more direct: "Yes, of course, we have treated quite a few." Katja then wanted to know what happened if the cancer was not operated on: "Then the body deals with it itself. Its self-healing powers are constantly at work."

It is true that the body possesses self-healing powers that can make tumours disappear – sometimes even spontaneously, without treatment. But this little-researched phenomenon occurs rarely, as Herbert Kappauf, a cancer specialist who studied the phenomenon over two decades while based at Nuremberg Hospital, makes clear.

According to him, spontaneous remission occurs in fewer than 1 of 100,000 cases in most forms of cancer. He studied 35 cases and points out that no studies to date have shown that patients or doctors can cause cancer to spontaneously go into remission.

Many of the alternative practitioners told us about patients with terminal cancer whom they had cured. One such was Ralf Brosius, who believes he owes his own life to the wild plant juices promoted by John Switzer.

A former cancer patient, Brosius makes a living from the story of his miraculous cure, selling vegetable concoctions, giving talks and appearing on talk shows. A journalist looked into his story on our behalf. She found that his cancer had not been terminal, as he claims, but had been diagnosed at a much earlier stage. Two doctors who specialise in this form of cancer agree that it was not Switzer's wild plants that cured him, but surgery. When this was put to

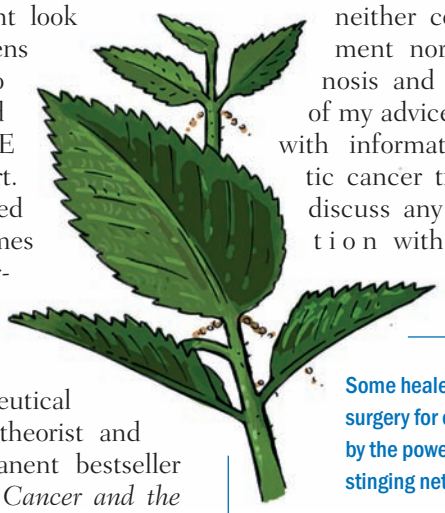
him, Brosius' terse response was: "Who am I to contradict an expert? A doctor should know better than me."

The legality of their recommendations is clearly a concern among some doctors and naturopaths. We often heard statements to the effect that, as healthcare professionals they were obliged to recommend surgery, chemo- and radiotherapy, but as individuals they would advise otherwise. Some referred us to an informed consent form that we would need to sign before beginning treatment, so that they would not be legally liable.

Just what such a sophisticated legal document might look like, and what happens if you don't want to sign, we discovered for ourselves at the 3E Centre in Stuttgart. The centre was founded by one of the big names on the radical alternative medicine scene, the former male nurse Lothar Hirneise – a pharmaceutical industry conspiracy theorist and author of the permanent bestseller *Chemotherapy Heals Cancer and the Earth is Flat*. The man who showed us round the centre told us that Hirneise was now setting up a centre in Poland. "He taught us that there are no 'patients' here, only 'guests'."

They all undergo the same "3E programme", based on a cancer diet, various "detoxification" methods and "energy work". Five weeks at the centre would cost €10,283.

When we asked the 'Medical Director', a naturopath, to look at Katja's diagnostic findings, she said: "I'm afraid I can't, as I would become legally liable. I can't give you any advice without your signature. Our approach is so radically alternative that we always have one foot in prison." We were required to sign a form which, put plainly, released the Director from her professional responsibilities. It included the statement, "Cancer can be cured." The following paragraph read: "By signing this form, you confirm that I have explained to you that I will neither conduct any treatment nor make any diagnosis and that the purpose of my advice is to provide you with information about holistic cancer treatments. Please discuss any further intervention with your treating doctor, naturopath, psychologist or other therapist."



Some healers advise against surgery for cancer and swear by the power of nature – as in stinging nettles, for example.

Katja was outraged. The naturopath retorted: "I sense a lot of insecurity in you. Most guests here don't have a piffling little tumour, but a devastating diagnosis. And they know what they want…" The women's voices took on a shrill note, and red blotches appeared on the neck of the naturopath. She assured Katja that she had just recently helped two breast cancer sufferers, who were now free of cancer, having followed this path with her. When I asked her to confirm that they were cancer-free and had not had surgery, she replied, "Certainly, using the 3E programme!"

The co-founder of the 3E Centre, Klaus Pertl, a mental coach according to his own website, hurriedly joined us and tried to mediate. He was about 50, with a receding hairline, greying at the temples, a sonorous voice and a jovial tone. The naturopath retreated, but he said: "It doesn't matter to us what tumour you have. You must feel comfortable here, and can't expect us to destroy the tumour in two days. After leaving here, you will need to follow our programme for a further nine months at home. That is how you can 'resolve' cancer – rather than just destroying the tumour."

The myth of 'dangerous surgery'

The practice of the hard-line surgery sceptic, John Switzer, on Lake Starnberg in Bavaria, is nothing like what you would normally expect from a doctor's surgery. The receptionist, all in red and dripping with gold chains, sat in a cubicle plastered with posters with headings like *Wild Plant Calendar or Quantec Medicine from the Future*. The doctor scrutinised Katja and told her: "You have irritated the tumour by having a biopsy. If you were my sister, I would have advised you against it." He then added that this increased the risk of the tumour spreading, which is why

The 'Medical Director' declined to look at Katja's pathology report: "I'm afraid I can't, as I would become legally liable"

Alternative medicine practitioners cherry-pick what suits them and ignore the rest

surgery would be dangerous.

This controversy is as old as medicine itself. Around 400 BC, the Greek physician Hippocrates recommended leaving tumours alone, as surgery would only hasten the course of the disease. Five hundred years later, the Roman physician Galen, who coined the term 'cancer', wrote about the first successful cancer operations in history. Over the next 1800 years, it continued to be a matter of debate. In 1882, the US physician William Halsted performed the first full mastectomy on a breast cancer patient. This marked the start of the triumph of the surgical approach.

But it didn't silence the sceptics. Even at the start of the 20th century, there were clinical trials where cancer was allowed to run its 'natural course' in patients. After five years, only a small percentage of these patients was still alive, if any. The surgeons refined their methods, and most surgery is now breast-conserving. New studies have consistently confirmed higher survival rates following surgery, particularly when performed at an early stage – most of the alternative medicine practitioners we talked to, however, still consider surgery as dangerous as Hippocrates did.

To support his position, John Switzer handed us an article from a magazine, saying that "eminent cancer researchers" had confirmed this. I checked the sources and traced them back to the epidemiologist Michael Retsky, from Harvard, who has spent many years researching the hidden dangers of cancer surgery with a top-level international team of experts.

He suggests that, under certain circumstances, operating on cancer may prematurely awaken "dormant metastases", potentially shortening the life expectancy of some patients. This could happen due to inflammatory substances being released by the body in response to surgical wounds. The scientists were in no way rejecting surgery, however. Their proposed solution was amazingly simple and does not fit with the conspiracy theories of many alternative practitioners: they suggest using off-patent drugs related to aspirin that suppress the inflammation.

Based on this study, John Switzer advised Katja against surgery. Just to be absolutely certain, I sent the authors of the study the information about our tumour. Their answer could not have been clearer: co-author Romano Demicheli urged the patient to undergo surgery immediately, adding that "Those charlatans should be prosecuted."

This is a pattern I often encountered in my research. Conventional medicine puts forward theories, discovers new treatments, rejects them or researches them further. Alternative medicine practitioners cherry-pick what suits them and ignore the rest. They then construct a whole mass of conspiracy theories, always centred around the pharmaceutical industry, which is an easy target that offers plenty of scope for attack. This is how they make patients feel they are on their side.

Apricot kernels are considered by conspiracy theorists to be a panacea against cancer, due to their active ingredient, amygdalin (also known as vitamin B17). Conventional medicine practitioners, however, warn that they can be fatally poisonous. The truth is somewhere in the middle; the most recent research shows that their toxic effect has probably been exaggerated and that the ingredient does act against cancer, at least in cell experiments. Caution, however, is still advised.

The miracle treatments

Our two-and-a-half-hour discussion with Dr Richard Huthmacher must rank as one of our most absurd experiences in the jungle of miracle healers. He received us in the foyer of a four-star hotel. He was around 60, with a well-trimmed beard and wearing a dark suit and two chunky earrings, one black, one white – he later spoke about "black and white magic". The treatment he proposed broke all records for speed: two days for €2500 per day. If it didn't

work, he said, you could always opt for surgery. The concept was a mixture of psychotherapy, hypnosis and a "return to childhood". According to Huthmacher, the treatment worked at the level of the individual atoms of cancer cells. Using his spiritual energy, he could influence the "spin of the electrons" – "quantum healing" to be precise. Of course, it wasn't something that you could grasp immediately. It had taken him 20 years to get his head around it.

The methods employed by the other therapists were more rooted in reality. Discussing their effectiveness would take a book. Many treatment approaches can usefully supplement conventional medicine, and some of them have been intensively researched for decades. But there are often good reasons why they have so far not proved effective.

A case in point: four doctors offered us "local hyperthermia", a procedure in which cancer cells are exposed to temperatures of 42–44°C using radio waves, and are destroyed – that's the theory anyway. According to Peter Wust, radiologist at the Charité university hospital in Berlin, who has been researching hyperthermia since 1988, the principle is simple and, if it worked, would offer a useful supplement or even an alternative to chemo- and radiotherapy. "There's just one problem," he continues. "As the heat penetrates the body, it falls dramatically." They have done the measurements and shown that it's not possible to achieve the target temperature in most tumours. In his opinion, therefore, the potential usefulness of local hyperthermia will be restricted for the time being to tumours that lie close to the body's surface.

Ginseng capsules are a bestseller in pharmacies and health food shops. It is really a plant that has many effects and its importance for cancer sufferers needs to be researched further. In the body, however, it has a similar action to oestrogen. This means that hormone-dependent breast tumours grow more rapidly under Ginseng treatment. Do not take Ginseng before consulting a qualified doctor!

The alternative practitioners did not mention any such research results – they let us believe that doctors, in the pay of the pharmaceutical industry, were deliberately suppressing these methods. It was the same with immunotherapy. Alternative practitioners make it sound so simple: the cancer disguises itself to escape attack from the body's own immune cells and the immune system fails to detect the enemy within. This is all true. But while leading scientists around the world are in a thrilling race to find effective immunotherapies, the alternative practitioners claim that academic research is ignoring the links between cancer and the immune system. They recommend nutritional supplements and cancer diets to stimulate the body's natural immunity. "Some are useful to supplement conventional medicine, the effect of others is not proven or has been disproven," says Jutta Hübner of the German Cancer Society.

€7800 for vitamin C

The different treatments cost anything up to €30,000 in the first year. It was never easy to pin our selection of alternative practitioners down to a price. Only one of them had a contract with statutory health insurance providers, while two others suggested that private health insurers might possibly cover part of the cost. We got vague answers.

When, for example, I asked about the cost of high-dose vitamin C therapy, one doctor initially quoted us €75 for one infusion. It was only after dogged questioning that we learnt the treatment would only work over an entire year – at two infusions a week, this alone would cost €7800. Most of the alternative practitioners couldn't even give a rough estimate of the total cost, and often cited "other necessary tests" as a reason, which alone came to anything up to €1000 in total.

The "Höner Multiple Step Treatment" of one animal alternative medicine practitioner was a bargain by comparison, but he was reluctant to

The different treatments cost anything up to €30,000 in the first year

"Being so much the focus of someone else's attention is a wonderful feeling"

say more, as he was probably already facing legal problems. "I can't advise or treat any people," he told us. On the website alternativheilung.eu, a mix of various food supplements is recommended as 'self-treatment' for cancer.

Höner apparently discovered how very effective they were when he used them on his dog. He used to manage the website himself, but the legal information now gives the name of a woman who supplies anyone interested with a direct link to his product page. An anti-cancer package can be bought for about €170, enough for three months. In our phone conversation, Höner was induced to put a figure on the chances of success – something that the other alternative practitioners were careful to avoid, because this would not be legal without supporting scientific evidence. "Well above 90%, provided you haven't had any chemo- or radiotherapy. Much lower if you have," he told us.

The Swiss spirit healer wanted to be alone with Katja for the "energy work" on the tumour. The session lasted half an hour; no sound was audible through the door. Would she now, after seeing the findings, diagnose a malignant tumour where there was none?

Katja later described the experience to me. The healer placed both hands on different areas of the body – the chest, the armpits, the abdomen, with one hand always on the front and the other on the back, and held them in the same position for several minutes. Katja relaxed: "It felt as though energy was passing through me from front to back. My thoughts flew away. Being so much the focus of someone else's attention is a wonderful feeling. I went to sleep, a waking sleep, drifted off as I sat there, only occasionally being brought back to reality. You feel better because you have centred on yourself. That's not something you do every day."

Medicinal mushrooms have been shown to be effective against cancer in animal experiments. There are also a number of promising studies on their use in people with stomach and bowel cancer. Contrary to the opinion of some alternative medicine practitioners, however, mushrooms are not a substitute for conventional medicine.

The Swiss spirit healer had passed our test with flying colours. She'd interpreted the findings correctly, recognised the danger, told Katja to have surgery. She had also done her very best to support the healing process. The healing power of meditation and similar procedures is now a subject of research and it's the immune system – which suffers from the effects of chemo- and radiotherapy – that seems particularly to benefit from it.

The one fault: the spirit healer fell into the trap and felt a small, very aggressive tumour precisely where the X-ray indicated it would be. Nobody is impervious to the power of suggestion.

The shocking results of our research don't allow broader conclusions to be drawn about alternative treatment methods in general – this was a random sample of self-appointed cancer specialists. Nonetheless, it suggests that alternative medicine needs to be more strongly regulated.

Opponents argue that everyone has the right to make their own decisions about their body. But leaving it entirely up to the individual, sending them out into the world of miracle healers without reliable advice, is expecting too much of any layperson.

Katja agrees. "The thing that most gets me is that everyone acts as though they are offering the best thing around, and then tells you that it's your decision." Any cancer patient who innocently enters the jungle of the miracle healers is taking a gamble. If they end up with the wrong one, they risk an early death. ■

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