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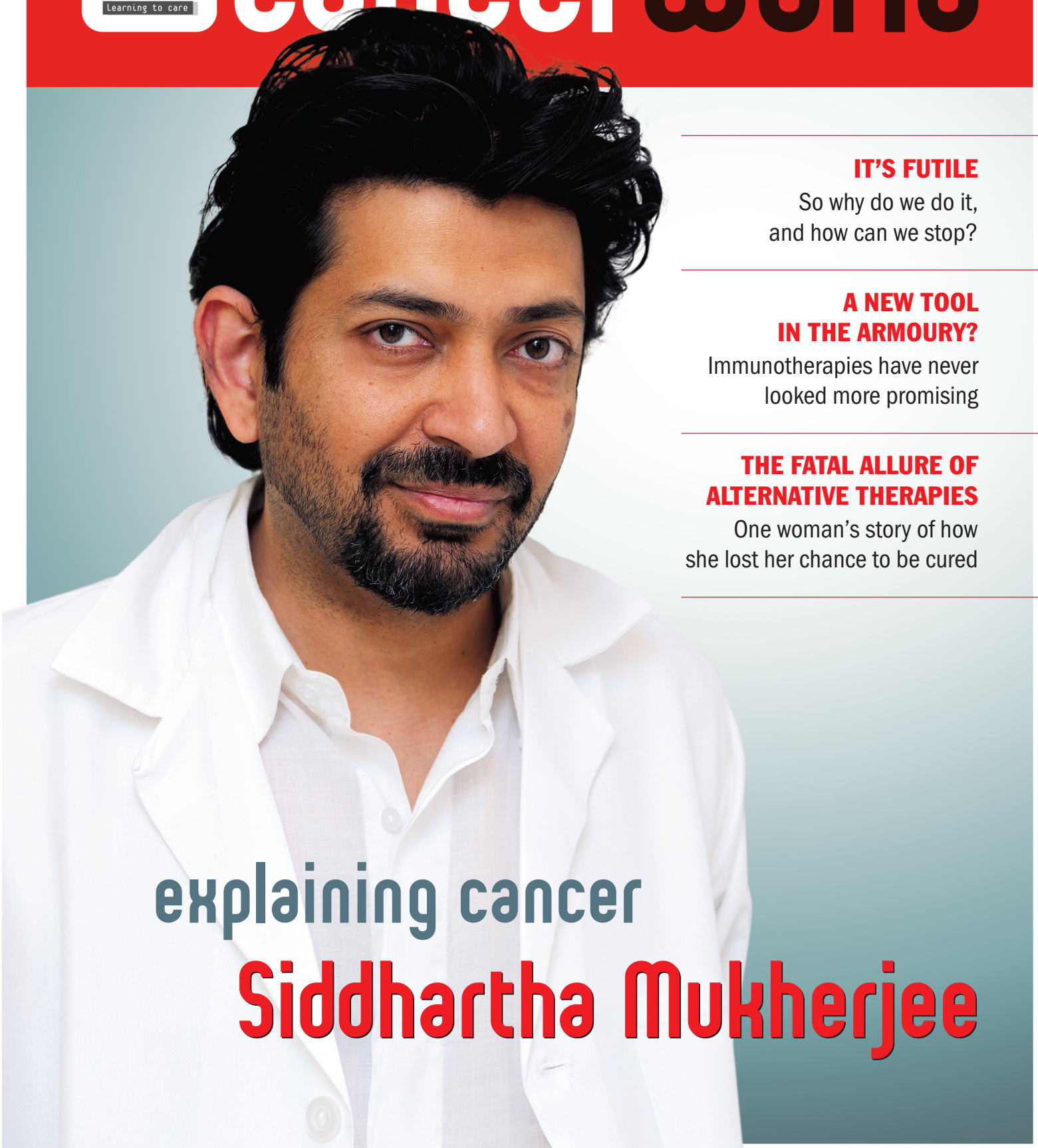

IT'S FUTILE

So why do we do it, and how can we stop?

A NEW TOOL IN THE ARMOURY?

Immunotherapies have never looked more promising

THE FATAL ALLURE OF ALTERNATIVE THERAPIES

One woman's story of how she lost her chance to be cured

explaining cancer

Siddhartha Mukherjee

cancerworld
Shaping the future of cancer care

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

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Personalised medicine: a note of caution

KATHY REDMOND EDITOR

Tailoring a patient's treatment to the particular biology of their cancer holds out the enticing prospect of avoiding over-treatment and reducing unnecessary toxicity – patients and cash-strapped health systems both stand to benefit. But delivering the right option for the right patient at the right time takes more than having the right biomarkers. And success in developing predictive biomarkers and targeted drugs has so far been modest when compared to the time, money and effort invested.

All of which gives cause for concern that so many people are jumping on the 'personalised medicines' bandwagon and are pushing national and European policy makers to make this a priority.

The problem lies not with personalised medicine *per se*. Medicine has always been about tailoring treatment and care to a patient's particular disease, age, comorbidities and preferences. The problem is that when the term 'personalised medicine' is used today, the focus is on one aspect of tailored cancer treatment – the use of targeted drugs and predictive biomarkers.

We know that translating scientific know-how into clinical reality is a highly uncertain business. History is littered with scientific failures that once appeared highly promising but ended up on the scrap heap. So far only a minority of cancer patients have derived significant benefit from targeted drugs, and that is not likely to change much in the immediate future. Arguing in favour of putting all our eggs in the 'personalised medicine' basket is therefore a flawed strategy that risks creating unrealistic public expectations.

It also takes the focus away from addressing obstacles to delivering personalised care that we do know how to overcome. Much more public funding is needed to conduct the optimisation studies that can show how best to use the the therapies we already have. Then there is the question of delivering personalised cancer care in everyday practice. Urgent action is required to improve cancer services, so every patient receives the attention of the right mix of specialists, to plan and deliver care tailored to their needs.

And finally, while we certainly need to vigorously pursue the potential for developing therapies designed using our knowledge of cancer genetics, the current heavy focus on drugs is too narrow. What about the potential for more precise tailoring of surgical and radiotherapy strategies, which currently account for only a tiny fraction of research into personalised therapies?

We need to be careful about the messages we send out. The biggest potential for improving cancer outcomes over the coming years lies in redesigning health systems to give all patients, regardless of cancer type, access to high-quality treatment and care from a multidisciplinary team of specialists. If we call for policy makers to focus instead on a scientific potential that might never reach the mainstream, we risk giving them a green light to shirk their duty to do what they must do to improve the delivery of cancer services. CW

Siddhartha Mukherjee: explaining cancer

ANNA WAGSTAFF

With our new-found understanding of cancer biology comes the opportunity to explain a disease that for centuries has confounded doctors and engendered stigma and superstition. Siddhartha Mukherjee took that opportunity and turned it into a best seller.

Just who is Siddhartha Mukherjee? This is the question many veterans of the cancer community asked as a book by this unknown author began to win critical accolades and prizes last year, including the Pulitzer Prize for non-Fiction and the Guardian First Book Award, earning Mukherjee a place among TIME magazine's 100 most influential people.

Less than two years since publication, *The Emperor of All Maladies: A Biography of Cancer* has sold between half a million and a million copies, is being translated into 20 languages, and continues to generate around 50 emails to the author a day. "I was completely overwhelmed by the generosity of the response," says Mukherjee, currently a practising oncologist specialising in haematological cancers at the Columbia University Medical Center in New York City. "By the size of it, by how diverse it is, by how diffuse it is. From students and general lay readers who said 'I was never interested in this question till I read the book,' to scientists at the National Institutes of Health who write thanking me for providing an overview. Different people come at it in different ways. For some people it gives them solace, for some it activates them. Young men and women write and say 'I now want to be a scientist, a cancer researcher'. This happens literally every day." His celebrity status is such that he was even approached by a group of students while on a trip with his kids to Disneyland.

Reading Mukherjee's own biographical notes will tell you that he reached his current position as assistant professor of medicine at Columbia University, in charge of a translational research lab at the University's Irving Cancer Research Center, through an academic research route, with the clinical practice coming only later. Born and educated in New Delhi, India, he went on to major in biology at Stanford University, California, where he worked in Nobel Laureate Paul Berg's laboratory defining cellular genes that change the behaviours of cancer cells. A Rhodes Scholarship took him to Oxford, where he earned a DPhil in immunology. Only then did he train as an MD at

Harvard Medical School, where he completed his residency in internal medicine followed by an oncology fellowship at Massachusetts General Hospital.

His research focuses on the links between normal stem cells and cancer cells, specifically probing the microenvironment of stem cells – particularly blood-forming stem cells. It has attracted grants from many sources including a coveted Challenge Grant from the National Institutes for Health, and generated papers published in journals including *Nature*, *Neuron* and the *Journal of Clinical Investigation*.

Mukherjee, then, could be summed up as one of the new generation of translational researchers who is exploring one of many interesting avenues that may offer new opportunities for intervening in processes that generate and fuel certain types of cancer growth.

None of this, however, offers a clue as to why he ended up being the first person to explain to a mass general readership the nature of this frightening, maddeningly elusive, multifaceted enemy that for millennia has had doctors, cancer patients and society at large

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asking: what is this thing we are up against?

For Mukherjee, however, the real question is why no one else had already done it. "When I was training as a fellow in cancer medicine what was amazing to me was that such a book didn't exist. Here is a family of diseases that will affect one in two or three of us, and we don't have a sense of what brought us to this point and what we might be doing next. So that is how the book began to be written. But my approach to this wasn't to write a 600-page book. Really I began to keep a journal; it was a very personal journey for me to start with."

It didn't take him long to realise that his need to understand was shared, even more urgently, by many of his patients, and the book then also took on the task of trying to respond to their needs.

"Every time you treat a patient in the hospital, once you've allowed them to get used to the madness that modern medicine is, the first question patients want to know is: Why do I have this? What is going on? What do I do next? That is their first mechanism of grappling with the disease, long before diagnostic tests and therapeutics kick in."

If people don't get an answer they can make sense of, says Mukherjee, they reach out for other explanations, which can range from nihilism – cancer is too complex, too evasive; nothing can be done – to conspiracy theories. He recalls a talk he gave at a healing retreat for women with breast cancer, involving yoga and meditation, as "one of the most hostile environments" he has ever been in. "The conversation went like this: 'Is it not obviously clear to you that there are abundant environmental carcinogens that you know and that I know are causing breast cancer? And if you know and I know, why have we not been able to change the world and remove these environmental carcinogens?'"

He often encounters patients who are convinced that pharmaceutical companies are hiding the real cure and are in cahoots with the government, or there are alternative therapies that will cure all cancers, but no one wants to invest in them and refine them. "These theories really abound across a swathe of this and other countries."

Understandably, says Mukherjee, these perceptions corrode the relationship between doctors and patients that is so essential to practice medicine. "As I point out in my book, there is reason to be suspicious. The relationship has been corroded in the past. But I hope the book provides a perspective across the centuries about the complexity of the problem, how it has been tackled, correctly and incorrectly, what

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"I made a point of trying to identify moments in which the vision occurs and then the vision becomes a block"

wrong roads we went down, and how we worked ourselves back."

The challenge of explaining such complexities to a lay audience may be one reason why no one has attempted such a book before, and this one certainly does not lack ambition. It took Mukherjee seven years from start to finish and it is no 'Idiot's Guide'. Among its more scientific passages, for instance, is a highly accessible, but nonetheless demanding, description of the mechanism of retroviral transcription. But by that point in the book the reader has already been drawn into a dramatised history of the breakthroughs and false trails by which the true nature of cancer was being revealed, in fits and starts, glimpse by glimpse, through a diverse parade of protagonists from specialisms ranging from epidemiology to biology, pathology, surgery, haematology, internal medicine, radiology, virology and genetics.

These individual stories are woven together into a tragic-heroic detective story, an odyssey where the trail frequently diverts up blind alleys, led there by gifted, dedicated and courageous specialists who are often too certain of their own vision to pick up and interpret clues that should have turned them in another direction.

The surgeons who insisted for decades, and without evidence, that the only reason for recurrences and metastatic spread following breast cancer surgery must be that they had used too small a margin, and the only remedy was to chop out ever larger chunks of their patients' upper torsos. The medical oncologists who, after the great initial breakthroughs using multidrug regimens to treat acute leukaemia and Hodgkin's disease went on to apply the same principles to advanced breast cancer, treating up to 40,000 women with extremely toxic therapies before discovering that the only evidence of benefit was generated from a fraudulent trial in Johannesburg. The geneticists who discovered the structure of DNA, which was to prove such an important part of the puzzle, but insisted that Nixon's proposed war against cancer would be a futile exercise until every last gene of the human genome had been decoded. The virologists whose discovery of the so-called "Rous sarcoma virus" in chickens lent credence to the theory that cancer is an infectious disease, leading to a fruitless decade of fevered searching for a single viral cause, which made little sense given the wider evidence.

Mukherjee describes his book as 'a manifesto for humility', and says he wanted to show that science doesn't exist in "some kind of an Arcadian realm of perfect truth and honesty", but is in fact a very human project, "and therefore susceptible to the same foibles that any human project is susceptible to: egos and mistakes and attachments to theories that then don't get unattached from your brain."

Every character in the book is real, he says, and shares the benefits, but also the paralysis, of being a visionary. "The vision becomes an obstruction. I made a point of trying to identify, to isolate, those moments in which the vision occurs and then the vision itself becomes a block. It's true of most of the characters of this book. They have the simultaneity of human genius and human flaws. It became a story of human beings trying very hard, and sometimes failing very hard, to work their way around what is clearly one of the seminal problems of the 20th century."

The book is not without critics. Many researchers question the choice of what to include and what to leave out of the book. "The lodestone was anything that made a difference directly in the lives of patients," says Mukherjee. "Someone asked me: What about telomeres? I said that is a very interesting theory and it will make itself into this book when you find me the first medicine that can modify telomeres in a real human being and make a difference in their lives. Even what about Avastin? If you were writing about macular degeneration, that book would have to have a central role for a drug like Avastin. But has Avastin really changed the way we think about and treat cancer? Not really. It was a wonderful theory, and then met the ugly facts. Does it make a huge difference? No. Not in breast cancer and barely in colorectal cancer."

Mukherjee has also faced criticism for choosing

"My take on this is that you had to be a non-expert to write this book. It is crucial."

to call the book a biography, on the grounds that it anthropomorphises cancer, attributing to it characteristics of an animate enemy rather than a biological phenomenon. "It's created quite a backlash," he says, "though there is no sentence in the book that does any of that except when quoting people talking about their illnesses in very human and personal terms."

And while the book has certainly been widely welcomed by the oncology and science community, there may also be a hint of regret among some who were centre stage during many of the most exciting years, that this extraordinary tale of human endeavour ended up being told by someone who had not been there at the time. "My take on this is that you had to be a non-expert to write this book. It is crucial. You have to have the vulnerability to write without having to say you are the big expert." He points out that many of the most moving and seminal books in medicine recently were written by people who are relatively young to the field. "Atul Gawande, writing in the *New Yorker* about surgical error, wrote that as a young resident in surgery, just after his fellowship, because he could see that world for what it was, with fresh eyes."

Ironically, perhaps, the book Mukherjee wrote as a 'non-expert' has propelled him onto the A-list of invitees to speak at countless seminars and conferences. Having outlined so elegantly the human obstacles to making progress, surely he can offer some solutions?

He does not duck the challenge. The big issue right now, says Mukherjee, is converting the tremendous gains of scientific research into human medicines. "The level of diversity that has been revealed even within one cancer let alone across cancers, and the level of evolutionary pressures that are operating in a single cancer cell would have left someone from the 1950s shocked. So we have all this knowledge, and the public is asking, and we are all asking: where are the medicines that come out of this knowledge?

"I talk in the book about this metaphor that science inevitably produces a boil that lets itself out as steam through technology. But if you are living in the world of cancer, there is a lot of boil, especially from the basic science world, but there is little steam which would make the engine move. So the question we are asking ourselves is: Where is it? How can we transform breast cancer so that we can treat, say, triple negative breast cancer in a way that we could not even have imagined four or five years ago."

One problem, he argues, is a lack of innovation from the pharmaceutical industry. "I'm waiting for good exemplars of this change in which the drug emerges from research performed primarily by biotech or pharma companies. I've yet to see that. The reality typically still remains investigator-initiated trials or protocols. The drug company possesses some IP [intellectual property rights] around a molecule and investigators around the world go to the company and say, look you have this molecule, allow us to test it in a particular disease. Then if there is something real there it catches fire. But the initiative still lies with the clinicians and translational researchers, even today."

Comparisons that have been made with other industries with a similar focus on turning academic knowledge into marketable technologies – the IT industry for example – Mukherjee finds unilluminating. "It reduces the problem of cancer to a systems analysis and information systems problem, which it isn't. It is vastly more complex." And he doesn't buy into the idea that progress is being strangled because commercial secrecy is tying up vital information. "It would be possibly if there were dozens of things out

"We have all this knowledge, and the public is asking: where are the medicines that come out of it?"

there to be secretive about. It's not clear to me that we have that level of innovation yet. Pharma keeps telling us it has things up its sleeve that are deeply transformative. I haven't seen them."

He concedes, however, that these things can take time. "The claim is that a lot of innovation is going on within the pharma universe, but we can't see it because by its very nature it's hidden. Fair enough. Let's say it happens in about a decade. The clock has just begun. We will find out if it is true or not."

More and deeper understanding of cancer biology will of course continue to be important, but this is not where the blockage lies. What is needed now, says Mukherjee, is to bring more talented chemists into the field to help answer the question of how to intervene in the potential targets that have already been identified. He expects a strong contribution to this effort will come from the pool of expertise that is developing in India and China, among other emerging economies. "Hopefully they will bring a whole new wealth of ideas, chemical ideas."

Ironically perhaps, the other area of expertise that Mukherjee argues is becoming increasingly important in developing new drugs comes from the traditional skills of the clinical practitioner. "You need better old medicine to understand new drugs. Your clinical skills have to be more astute than ever, because the variables have become so complex. That was not the case when you were giving cytotoxics. Now you are intervening on extremely specific aspects of human physiology and you need to know how to follow those." He cites the example of the doctors who first began to notice a correlation between rash and response in the EGFR-inhibitor Erbitux (cetuximab). "You need a very astute physician to pick that up and say, 'There is something here. This rash out of the hundreds of rashes that happen to people on chemotherapy, seems to have something to do with response.' This has initiated a whole new field of understanding."

The development path of the mTor inhibitor everolimus (Afinitor) is another good example, he says. "The phase I people who first tested the drug on patients with kidney cancer said 'It's not as if the drug were melting the tumour away, but we see these patients coming back, they feel better, they look better and their disease looks stable. There's something there.' In the old days of chemotherapy, you would say, 'This is a nonsense intuition.' This would be precisely the drug that you would discard."

The BOLERO trial of Afinitor used in patients with advanced hormone-receptive breast cancer, who are resistant to endocrine therapy alone, is one of the few that Mukherjee admits could turn out to be 'transformative'. Calling up a graph comparing progression-free survival between those on an endocrine inhibitor alone and those additionally given the mTor

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Remembering the lessons of his own book, Mukherjee is careful not to get too carried away

inhibitor, he puts his finger between the two curves. "It fits the famous 'Bob Mayer rule' [named after the eponymous Harvard professor at the Dana-Farber Cancer Institute]: if you can put a finger between the two arms it is real, if not you might as well discard it. We need more of these things that really make a big difference in survival."

He is also excited about GlaxoSmithKline's trial combining BRAF therapy with immunological therapy against melanoma. "This is an obvious idea, seeing what will happen if you can combine targeted therapy and micro-environment-directed therapy or immunology-directed therapy. Presumably the immunology-directed therapy will have completely different pathways and be non-redundant with targeted therapies that are autonomous to the cancer cell. This is the kind of stuff that really excites me."

Remembering the lessons of his own book, however, Mukherjee is careful not to get too carried away. As he says, the reality is that there are more women who have been cured or benefited from "boring old chemotherapy" for early breast cancer than any targeted therapy for any cancer. "The question is: where are we going? Have we made another mistake? Are we wrong in thinking that the way forward is to target the cancer cell? Maybe five years from now we will conclude that this is not the best way to go. But you cannot go somewhere else without being here now."

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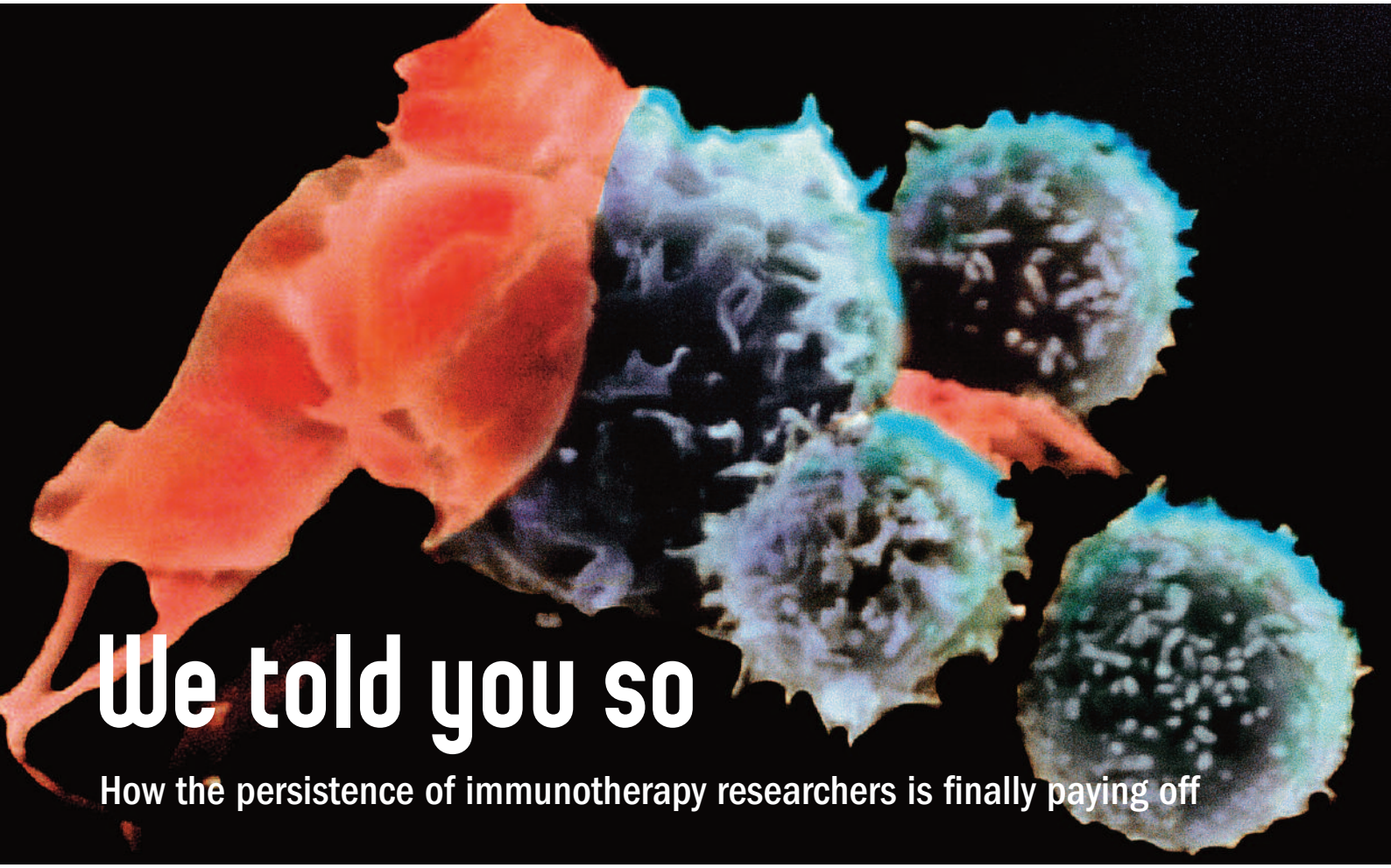
Mukherjee himself seems to accept no limits on his intellectual curiosity. In mid April the *New York Times* magazine carried a feature piece he wrote on the science and history of treating depression, titled 'Post-Prozac Nation', where he applies his detective writing skills to trying to make sense of another journey of scientific discovery that has been marked by great hopes of a magic bullet followed by disappointment, conspiracy theories and distrust.

At the same time, he has taken great care to sustain his hands-on clinical practice, though this has been tricky in the wake of his new-found fame, to the extent that he finds it very hard to keep his clinical and research agenda on track. Overloaded with requests from people wanting second, third, fourth or even fifth referrals, he took a pragmatic decision to remove that pressure. While he takes his turn caring for patients on the ward, he has moved his entire clinical practice to the 'fellows' clinic', which is run for people with no medical insurance and often no proper legal status. "Not because I'm a saint," he hastens to add, "but because it wipes the slate clean of all the access issues."

Mukherjee does not encourage discussion of his background or family, though the wide use of literary allusions and the general accessibility of the structure and style of his writing has, rightly or wrongly, been at least partially credited to the influence of his artist wife Sarah Sze, and he clearly revels in intellectual stimulus from almost any direction. He talks of himself as having multiple lives, "or at least dual lives," centred around patients. "Every time I think about anything that is relevant, for instance trying to understand how we ended up with this hypothesis of depression in 2012, and what the next steps are, I go back to patients. So this life is very important for me. It keeps me alive and it keeps my brain alive in a way I have to protect, otherwise I cannot keep working on other more abstract things." CW



We told you so

How the persistence of immunotherapy researchers is finally paying off

MARC BEISHON

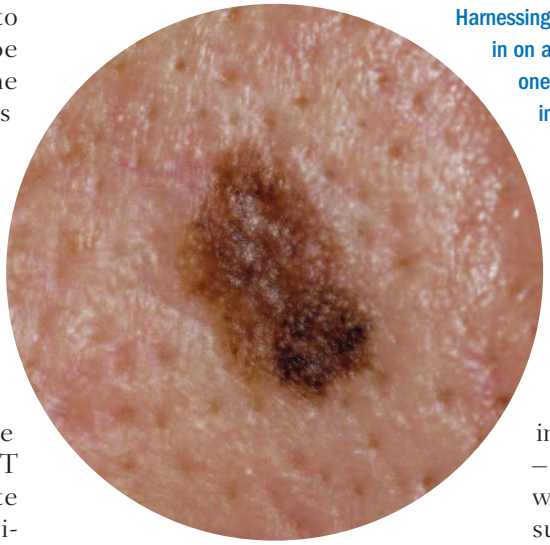
With two novel immunotherapies approved and many more in the pipeline, is it time to announce that a new treatment modality has emerged?

A class of therapy that has long held promise for treating cancer patients may finally have come of age. Immunotherapy, or biological therapy to give the broadest term, can use the body's immune system in a wide variety of ways, by directly attacking tumours, controlling factors that allow tumour growth, using vaccines to prevent but also to treat cancers, helping repair damage from other treatments, and more. Now, after more than a century in which the tantalising possibilities for harnessing the immune system to fight cancer have commanded sporadic interest but only limited success, a flood of recent research findings have earned their place in top journals and ASCO presentations, with promising trial results and a big pipeline of new agents.

Investment analysts, never slow to spot trends, suggest we might be approaching a tipping point – the number of ASCO abstracts on this topic more than doubled over the last two years, reaching more than 300 this year. Researchers now talk of the 'end game' being in sight for immunotherapy, though there is still a long way to go. The excitement that is building was triggered in no small part by the approval in 2010 by the US regulatory body, the FDA, of the first vaccine therapy, sipuleucel T (Provenge) for advanced prostate cancer, followed last year by ipilimumab (Yervoy) for metastatic melanoma, which is an 'immune-targeted', or stimulatory, antibody agent.

Meanwhile the wider public are being primed about the possibility of a major breakthrough. This April, *The New Yorker*, a literary magazine, carried a story titled 'The T-cell army', in which writer Jerome Groopman traces the early history of immunotherapy back to William Coley, a surgeon in New York, who stumbled on a case where a streptococcal infection seemed to help a sarcoma patient eliminate his cancer, and then tried to replicate it.

T cells – a type of lymphocyte, or white blood cell, found in the blood and other parts of the body – work mainly by producing proteins which allow immune system cells to communicate with each other, and which can also attack foreign or cancerous cells. It is the discovery of one type of T cell that produces a protein called cytotoxic T-lymphocyte antigen-4, or CTLA-4, that Groopman describes in detail, as it led to the development of Yervoy.



Harnessing the immune system. *Far left:* T cells home in on a cancer cell. *Left:* Melanomas like this one were the focus of much of the early immunotherapy research, but trials are now ongoing for a range of cancers

The breakthrough moment came when Jim Allison, head of tumour immunology at Memorial Sloan Kettering, and colleagues, spotted that the mechanism worked in the opposite way to what had been believed – CTLA-4 had to be blocked, not stimulated. It then took a while before they finally persuaded a drug company to take up the approach.

Drug companies could be forgiven for being cautious, given the long history of difficulties. Interleukin-2 (IL-2) and interferon-α – the mainstays of attempts at improving immune responses introduced in the 1980s – both have significant toxicity and limited evidence for overall survival. The past few years have also seen high-profile failures of companies such as CancerVax and Cell Genesys. But this unpromising picture has changed dramatically over the last two years.

There are two reasons why immunotherapy has now gained such traction, says Christian Ottensmeier, professor of experimental cancer medicine at the University of Southampton in the UK. "We've had a poor understanding of how the immune system works – but that is changing rapidly with work on chronic infectious diseases such as malaria, TB and HIV, as well as cancer – they are cross-fertilising and similar questions are being asked. Second, our tools are much better – we had quite rudimentary ways of looking at immune response, but in the past 10 years there has been an explosion in what we can deliver for measuring immunity. Being able to measure in more detail the different facets of the immune system, and in ways that others can reproduce, is a major contributor to the field."

As a result, he adds, we are now in a better position to study one of the least explored approaches that have the potential to improve outcomes for cancer patients. "There is also a rapidly accumulating body of evidence to indicate that immune attack on cancer is critical, and looking at it just numerically in the tissue is a very powerful tool for predicting outcomes – so there is a strong argument that improving outcomes can be achieved through improving immune responses. And there is a

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"In the past 10 years there has been an explosion in what we can deliver for measuring immunity"

"The field has changed in just two years from having little to offer to being a 'grown up' treatment"

rapidly growing number of randomised phase II and III studies that show this is actually the case. The field has changed in just two years from having little to offer to being a 'grown up' treatment."

Joost Lesterhuis, a medical oncologist and researcher at Radboud University Nijmegen Medical Centre, in the Netherlands, says that the basic research community had not lost faith with immunotherapy. "There have been a lot of papers in preclinical and translational research journals – there was a difference in perception about what immunotherapy can do between clinicians and laboratory scientists." A string of high-profile negative trials, in particular with vaccines, has not helped of course, but there has been steady refinement of animal models and a flow of small human studies that paved the way for the impact we see now, with the standout sector being the novel immune-targeted agents such as Yervoy, says Lesterhuis.

He outlines some of the key advantages of immunotherapy. "It can be very specific – T cells can be directed against tumour cells, in theory without causing any damage to surrounding tissue. The immune system also has a memory, so if you induce a response, in general it is long-lasting and can be quite potent – we've seen instances in people with high tumour burden, although people with less tumour tend to respond better.

"And immunotherapy is additive – the old idea was that you should go for one treatment or another – now we are moving in the near future to giving immunotherapy with or on top of other therapies."

IMMUNE CHECKPOINT BLOCKADE

Ipilimumab (Bristol-Myers Squibb)	CTLA4-blocking antibody	Melanoma	Approved
		Prostate cancer and NSCLC	Phase III
		Other tumours	Phase I–II
MDX1106 (Medarex/ Bristol-Myers Squibb)	PD1-blocking antibody	Melanoma, RCC and NSCLC	Phase II
CT011 (CureTech)	PD1-blocking antibody	Melanoma and haematological malignancies	Phase II

VACCINATION STRATEGIES

Sipuleucel-T (Dendreon)	Autologous APC vaccine loaded with prostate acid phosphatase	Prostate cancer	Approved
Dendritic Cell (DC)-based vaccines	Autologous DCs loaded with tumour antigens	All cancer types	Phase I–III
MAGE3 ASCI (GlaxoSmithKline)	MAGE3 protein	NSCLC	Phase III
PROSTVAC (Bavarian Nordic)	Poxvirus-based PSA-targeted vaccine	Prostate cancer	Phase III
T-VEC (Amgen) (developed by BioVex as OncoVEX)	Attenuated herpes simplex type 1 virus encoding human GM-CSF	Melanoma and HNSCC	Phase III

Source: All tables are adapted from W Joost Lesterhuis and Cornelis J A Punt (2012) Harnessing the immune system to combat cancer [poster]. *Nature Rev Drug Discov* www.nature.com/nrd/posters/cancerimmuno

Strategies in immunotherapy

Immune checkpoint blockade

Among the big news stories at ASCO this year were trials of two agents in the class of immune stimulatory antibodies, targeting the PD-1 (programmed cell death) and PD-L1 (programmed cell death ligand) proteins. The aim is to block pathways that shield cancer cells from the immune system, and the agents have been trialled not only in melanoma and kidney cancer, which have long been candidates for immunotherapy, but also in non-small-cell lung cancer (NSCLC), with promising results in these hard-to-treat advanced tumours. Both agents are made by Bristol-Myers Squibb (BMS), which also makes Yervoy.

The reason Yervoy has gained so much attention is straightforward, says

ADOPTIVE CELL TRANSFER

Adoptive transfer with TILs	Polyclonal T cells against multiple tumour-associated antigens	Melanoma	Phase III
Adoptive transfer with TCR-transduced T cells	Monoclonal T cells with high-affinity TCR against single tumour-associated antigens	Melanoma	Phase II

Lesterhuis: it is the first drug to show survival benefit in a phase III trial in advanced melanoma (although the BRAF inhibitor, vemurafenib, has competed for attention, and the two are being trialled together now). "It wasn't that most patients were cured – they weren't – but it was the first positive story to tell about melanoma, and there were dramatic responses in a minority, and it was the spark that made a lot of people enthusiastic again."

This type of immunotherapy is progressing very rapidly, he adds, because clinical data are becoming readily available, and because it is not a patient-tailored approach. "It's just an antibody against a surface molecule on T cells."

Therapeutic vaccines

Ottensmeier points out that there are well-established immune treatments, such as bone marrow and stem cell transplantation in haematological malignancies, but the spectrum of treatments is opening up widely now. In addition to agents such as Yervoy, he considers that therapeutic vaccines such as Provenge are becoming valid treatment options.

His opinion is shared by Lesterhuis, who co-wrote a review paper published August 2011 in *Nature Reviews Drug Discovery,* where they argue that therapeutic vaccines are more widely applicable than preventive ones, as most human cancers have several causal agents. Such vaccines can be developed in a variety of ways, using viruses, proteins, DNA, peptides, dendritic cells and so on. Some of these strategies are showing promise, they say, but most have failed. One important lesson they highlight from past mistakes is that enough time must be allowed to judge the potential impact of a vaccine in early-stage trials.

Despite the many setbacks, there is now a pipeline of candidates in phase III, such as GlaxoSmithKline's DERMA and MAGRIT trials for non-small-cell lung cancer and melanoma that target the MAGE-A3 antigen, and Amgen's talimogene laherparepvec (T-VEC), an engineered herpes virus that also targets melanoma. Ottensmeier adds that there are at least five randomised vaccine trials for lung cancer that are well worth watching.

Lab-grown T cells

Another interesting approach mentioned by Lesterhuis is adoptive T cell therapy. While the immune-targeted therapies and vaccines aim to induce or boost the body's existing responses to tumours, adoptive T cell therapies culture large numbers – potentially billions – of tumour-specific T cells in the lab, and infuse these into the patient. This strategy was developed in the US (for example in a trial in 2002 with advanced melanoma, although early work goes back to the 1980s), and has now started to become available for a few melanoma patients in Europe, at centres such as the Amsterdam Cancer Institute, Copenhagen University/Herlev Hospital in Denmark, and the Christie in Manchester, UK. The T cells can also be derived from blood or can be genetically modified, but in the main melanoma trials they come from the tumour – a treatment known as TIL (tumour-infiltrating lymphocyte).

The role of chemotherapy

The case is now being made that immunotherapy deserves to be classed as a distinct treatment modality, to rank alongside chemotherapy, hormonal

NON-SPECIFIC IMMUNE STIMULATION

IL2 (Novartis/ Prometheus)	Recombinant human IL2	Melanoma and RCC	Approved for melanoma in some and for RCC in most countries
IFNα (Schering-Plough/Roche)	Recombinant human IFNα	Melanoma and RCC	Approved for melanoma (adjuvant) and RCC in several countries
Denileukin diftitox (Ontak) (Eisai)	Recombinant IL2–diphtheria toxin conjugate	Persistent or recurrent cutaneous T-cell lymphoma	Approved in US; orphan drug designation in EU
		Other tumours	Phase I-II
Imiquimod (Meda/Graceway /iNova)	TLR7 agonist	Basal cell carcinoma, VIN and CIN	Approved for basal cell carcinoma; in Phase III for VIN and CIN
BCG	Intravesical administration of BCG as adjuvant	Urothelial cancer	Approved

"Benefit from both chemotherapy and radiotherapy may be related to immunological factors"

therapy and the new targeted therapies. But as usual with cancer, things are not so clear-cut. Take chemotherapy – as Ottensmeier says, "We are learning that both old and new chemotherapies that are not immunological in nature do produce immunological effects. Some think that chemotherapy is going to immunosuppress the patient, but that's not true for all drugs. For example, there is a recent paper in the *JCO* that found the number of immune cells in breast cancer predicted more benefit from chemotherapy. It means that when we have been focusing only on the cytotoxics in terms of poisoning cancer cells, it may be much more complex than that." The benefit from both chemotherapy and radiotherapy, he adds, may be related to immunological factors and not primarily to the toxic effects.

This is pointing to new directions for investigation with conventional treatments and with targeted therapies to find out whether they can work in conjunction with immunological treatment. "Some are particularly good and some really bad – we need a case-by-case analysis to understand the principles," he says.

Investigating the effects of platinum-based chemotherapies in combination with immunotherapy is Lesterhuis's own field and he's recently returned from a spell as a visiting scientist at the tumour immunology group at the University of Western Australia. "I've found that there are beneficial effects in induction of immunity, such as by activating dendritic cells, making tumour cells more susceptible to immune attack," he says. "It feels counterintuitive because one of the side-effects of chemotherapy is immune suppression with decreased immunity to bacteria, but in recent years we have evidence that immune response to tumour antigens is not decreased and may alarm the immune system towards cancer."

He points to another study, a phase II trial that has attracted interest, where Yervoy was combined with chemotherapy in non-small-cell lung cancer. "It showed longer progression-free survival depending on the scheduling of the two drugs, and phase III is now starting. The other exciting thing is that it is in lung cancer, which was thought to be a non-immunogenic disease." The anti-PD-1 agent has also shown some good responses in lung cancer, he adds.

Towards the end game?

But the successes so far should not disguise the many obstacles for making more progress in immunotherapy. While investigation and tools are developing fast, major gaps in knowledge remain regarding, for example, optimal dosage, scheduling and how to measure response. The rulebook for cytotoxic drugs is no good here; as Lesterhuis and colleagues point out in their review paper, maximal tolerated dose and tumour response rate have proved not to be valid as markers for immunotherapies, and there is much less – if any – correlation between drug exposure and efficacy and/or toxicity.

In particular, patients may take much longer to respond to treatments, and tumours may grow for a while. Benefits may not emerge for months or possibly years, which can leave oncologists and patients facing difficult decisions about whether to continue with treatments. Lesterhuis also notes that there can be unexpected side-effects, such as the high rate of acute renal failure that occurred in a trial of a combination therapy for kidney cancer. Generally, side-effects can be severe in immunotherapy, as found in trials of Yervoy, and can require fast medical action.

Inevitably, there are cost and regulatory issues concerning the new agents. When Provenge hit the headlines, it was on account of its price tag as much as anything else. Yervoy is not far behind, at about €85,000 for one course of infusions in the Netherlands, for example. A recently established cancer drugs fund in the UK is covering costs there, but at a 'tear-inducing' price, says Ottensmeier.

As with other therapies, there is a need to identify patients who will benefit. His own group presented a poster at ASCO on early work on a biomarker for gauging who might benefit from Yervoy for melanoma. Using a proprietary panel of tumour-associated antigens, they found that among patients treated with the therapy, those with pre-existing antibodies against two or more antigens were significantly more likely to survive. They concluded that the melanomas in these patients "are immunologically more visible", and so more likely to respond to activation of immunity.

Ottensmeier says that the current focus is mainly on treating established disease, but attention will also turn more to prevention of recurrence, and primary prevention and prevention of disease development – the HPV vaccine for cervical cancer being an obvious example of a primary prevention.

"And the excitement about anti-CTLA-4 is not only that it works in a small number of patients, but also that there is a group of patients who do not have recurrence after you've finished treatment, and it's a paradigm shift that I think we will see with vaccines and T cell transfer as well.

"It is a result of the memory of the immune system, both in B cells, which make antibodies, and T cells. They hang around for decades – probably for life. If they are enabled to see the tumour, then they can do what our current drugs have not been able to do." CW

ENLISTING 196 BILLION T CELLS TO HELP FIGHT STAGE 4 MELANOMA

When Hein Jambroers, a 47-year-old event coordinator from Roemond, a city in the southeast of the Netherlands, found a small mole on his leg that was growing, he went to his doctor, who sent him to the local hospital, where it was found to be melanoma. He then went to the university hospital in Maastricht for operations on his spleen and lymph nodes – but one year later, the cancer returned with tumours on his leg. This was summer, 2010. "I went back to Maastricht and they said they couldn't help me as the cancer was now in my blood. I went to Rotterdam too and was told again there was no treatment. So I started Googling."

Jambroers found the story of a Belgian woman who had been treated with ipilimumab in Brussels, and tracked her down on LinkedIn. After talking to her, and her oncologist, he was advised to see John Haanen at the National Cancer Institute (NKI) in Amsterdam, who was working on the latest melanoma trials.

"I was first put on vemurafenib [Zelboraf], the new BRAF inhibitor, and that worked well at first – a spot on my liver vanished and others shrank to a pea. But then it stopped working and tumours in my leg grew again, to egg size, within one month." He was then offered Yervoy, which had worked in other patients in Amsterdam. "I had four infusions but it didn't do anything – it is thought it could work after several months but there was no change in my blood work at all. I was told they were not expecting an anti-PD-1 trial before 2012."

He had already asked about adoptive T cell lymphocytes (TIL) in 2010, but had been told there were no plans to try it. Thankfully he then got a call inviting him to be one of the first three patients in the Netherlands to undergo the treatment, under Haanen.

Jambroers says that TIL is a major procedure involving several stages and people need to be physically fit. "First I had an operation to remove some tumour to get the antigen-specific T cells, but I got an infection and had to wait another month while that was treated. I then went back to have white cells removed from my blood and had a week of chemotherapy." That process – called lymphodepletion – is needed to eliminate competing lymphocytes and regulatory T cells. Meanwhile, the specific T cells were cultured for infusion – there were about 196 billion in his case, which he received in October last year. "I was told that 196 billion is an extremely high number of cultured cells – the results of all the worldwide TIL trials show anything over 150 billion gives a good chance of complete remission."

He feels that, even now, many doctors are still unaware of where to refer people

But the treatment was not over – he also had four infusions of IL-2, and had to go into intensive care as his liver and kidney began to fail. A week later, he was well enough to go home. A check revealed the tumours had shrunk by 25–30%, and he was soon back at work. "After another two weeks there was a 50% shrinkage, and by Christmas there were no active tumours – just one lump with fluid. By April this year it looked like I was cured – there was only scar tissue and nothing in my blood."

Jambroers, pictured here with his wife Varadi and daughter Jenna, has become an advocate for melanoma patients, telling his story on websites and in Dutch newspapers. There is much more about the latest treatments now available, but he feels that, even now, many doctors are still unaware of where to refer people. "I know how hard it is if you can't find information and I'm happy to tell my story whenever I can."

Futile care

Why does it happen, how can we avoid it?

Why are cancer patients being given medically futile treatment in the last weeks of their life? We hear this question raised time and again at international meetings and in journal articles, provoking polarised views and occasional acrimony.

A recent editorial in the *Annals of Oncology* (2011, 22:2345–48) posed the question: "Why are we not ceasing chemotherapy when it is useless, toxic, logistically complex and expensive?" It drew attention to studies showing marked global variations in approach between countries, with as few as 8% of patients in England receiving chemotherapy in the last month of life, compared with 37% in Portugal. And it commented that "Medical oncologists have overly optimistic predictions and, sometimes excessive, treatment-prone attitudes."

Is this a fair point? Are too many patients being offered aggressive treatments with unpleasant side-effects when palliative approaches would be the better option for their remaining days? Is the quest for new life-prolonging treatments overriding the best interests of individual patients?

Cancer World's Simon Crompton asked two experts – one a medical oncologist, the other a palliative care specialist – to debate the issue, and see if they could agree on a way forward.

Stein Kaasa

Palliative care expert and head of the Cancer Clinic at Trondheim University Hospital, Norway

It has been said that the intensity of cancer treatment may be related to culture, and this is backed by data that seems to indicate that culture influences the use of chemotherapy during the last two to four weeks of a patient's life. I believe this data needs to be evaluated and debated.

We can identify different cultural approaches to treating patients nearing the end of their life in different societies. Some medical oncologists offer end of life chemotherapy to as many as 15% – even up to 50% – of dying patients. Not all medical oncologists working within the same cultural setting will take the same approach, and the proportion of patients given futile treatment may vary between institutions and even within large institutions. Societies need to assess the cultural approach governing decisions about when to stop active treatment, from an ethical, clinical, practical and economic point of view, because the treatment being offered to patients is futile.

One factor may be that we do not have good enough indicators to select the right treatment for patients during the last three to six months of life. Improvements might be achieved by research focused on unselected cohorts of cancer patients during this part of their disease trajectory. Here oncology and palliative care would need to collaborate closely.

Matti Aapro

Medical oncologist and director of the Multidisciplinary Oncology Institute at the Clinique de Genolier in Genolier, Switzerland

It's well known that there are variations in treatments and the way certain situations are handled in different countries, but I have my doubts about generalising from such international comparisons, which are based on very diverse studies.

While it is true that attitudes may differ, it is not only the oncologist who dictates what happens – the attitude of the patient and their family is also crucial, and this may vary from country to country. I think the idea that medical oncologists are pressing ahead with treatments to the last minute in the full knowledge that they are futile is false. It is not always easy to determine what a 'futile' treatment is, or indeed when a patient will be 'at end of life'. In some cases we observe a rapid and surprising deterioration in the patient's status over days or a few weeks, often after a period when the disease has been progressing slowly with the patient remaining very fit. Is it 'futile' to try to find a new treatment for such patients?

If so, we should give up on treating endocrine-responsive breast or prostate cancer when it progresses following the first endocrine treatment. And we should not treat colon cancer that progresses beyond the first line of chemotherapy. And what about disease which may possibly be refractory to chemotherapy, as dramatically illustrated in the ☛

Annals of Oncology editorial? We know, for example, that many patients with non-small-cell lung cancer who have a poor performance status will not benefit from chemotherapy. But is that a sufficient reason to deny them a chance? The poor performance status may not be indicative of a major refractory tumour burden, and adequate support can help these patients survive longer, as was shown in a paper by Temel et al. (*NEJM* 2010, 363:733–742)

Oncologists recommend treatment in the full belief that it will bring positive results to the patient. It may not work out that way in practice, and may ultimately prove 'futile', but it is often impossible to know in advance.

One also has to accept that futility, while a statistical term, is not perceived in the same way by everyone. The distinction between treatment and palliative approaches can be false. Cancer treatments can also palliate pain, for example, even when they are not active against the disease. If you go through the literature on infused 5-FU chemotherapy, it is clear that in many patients the treatment reduces pain – an effect that might otherwise be achieved only with medicines that are less well tolerated. There are many other examples where treating the tumour reduces pain and other symptoms.

This isn't just about medical oncologists. Two other groups, in particular, are drivers in this issue, and the way in which they influence what happens to patients towards the end of life should be assessed by themselves and by society.

First, there is the pharmaceutical industry, which sells very expensive drugs to the patients via media advertising, talking about new 'breakthroughs'. These heavily marketed drugs have a marginal impact, if any, on patients who are in their last weeks and months of life, even though they might have remarkable effects when given to the right patient at earlier stages.

Second, there are the basic scientists who, via clever media coverage, create the impression that personalised treatment with new drugs and technologies will soon revolutionise cancer care. Theoretically they may be right, but there is a long way to go before we see a major influence on care for patients during the last three to six months of life, and systematic, large-scale clinical research on the use of these treatments in this setting is needed. Until then, the greatest potential to improve decision making about end of life care will come from more extensive and systematic use of good clinical indicators, including patient self-assessment of function, symptoms and psychological factors.

It is true that personalised treatments generally have fewer side-effects than chemotherapy, and bring good response rates and life prolongation to the right patients when used early in a non-curative disease trajectory. But there is an argument that patients are being encouraged to use these medicines for too long. Patients find it very hard to know what is best for them as their illness progresses, and I believe that medical oncologists need to be more careful than ever in making these decisions towards the end of life. It is very important that we raise the profile of this issue.

Industry is always blamed, but I am not sure that is fair. Poor journalism can certainly be at fault – which is why encouraging higher standards in reporting is so important. No one can deny that some recent developments in cancer drugs are of great value. But it is also true that statistically significant survival benefit of only a few days is of no clinical value.

As for the basic scientists' proclamations about revolutionary personalised treatments, it may well be that some scientists are "clever" in promoting themselves. But what about those clever drugs: imatinib, rituximab, trastuzumab, everolimus and others? Might not the new tools available today allow significant progress to be made in the individualised approach? It took years for some oncologists to accept that patients with endocrine-responsive breast cancer would derive little or no benefit from standard chemotherapy. Maybe the new tools will show which patients with non-endocrine responsive cancers will benefit from one or another drug class, beyond the classic determination of a HER-2 receptor for breast and some other tumours.

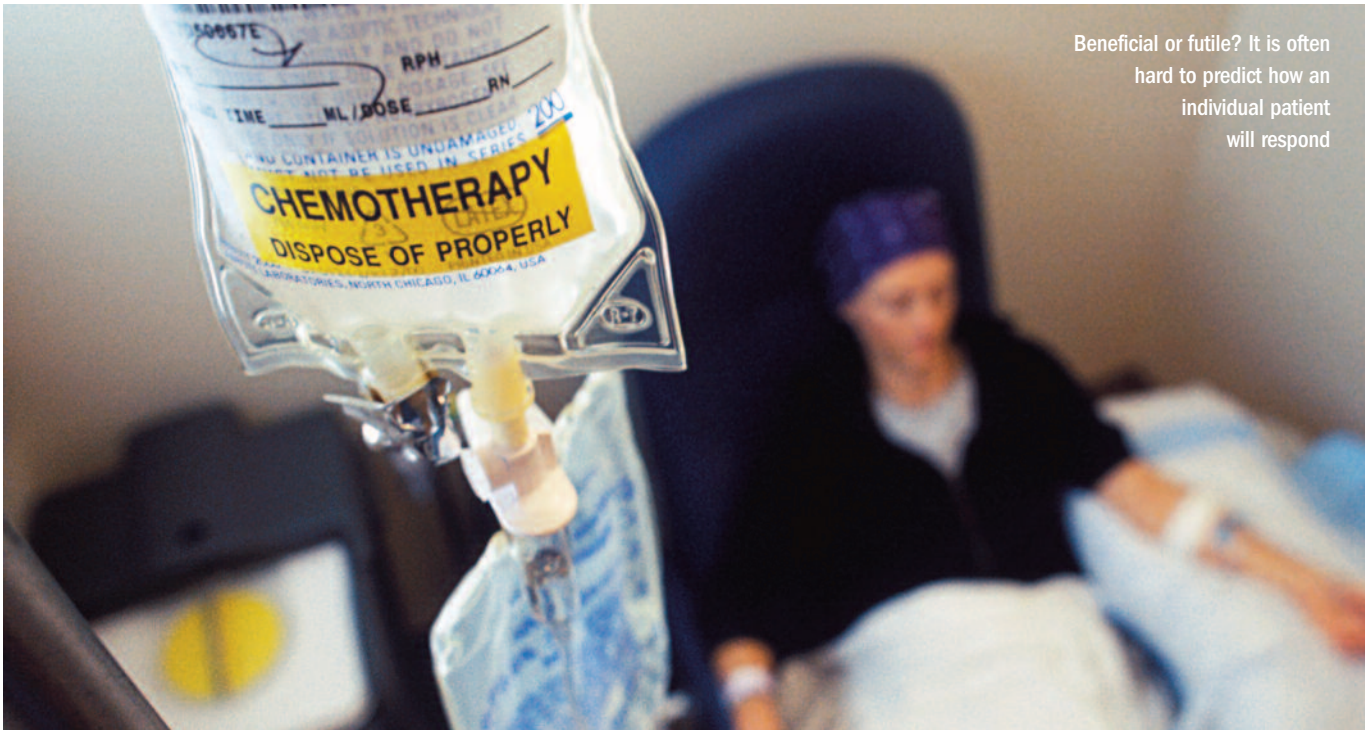
Oncologists want to offer optimal treatment for their patients, but they are subject to the pressure of marketing from industry, and at the moment I think the balance is wrong. There is no doubt that what physicians communicate, and how they do it, has a major influence on the decisions patients and their families take when approaching the end of life. We need a greater sense of realism applied to these decisions.

I think we need to go back to the individual patient, and ask ourselves who would really benefit from receiving this treatment. If you look at the inclusion criteria in the relevant clinical studies, most patients will have had a good physical performance status. So if a person's performance status starts to drop and/or their subjective symptoms increase, we should consider stopping treatment.

I believe you have to follow the patient – not just by their CT scans, but by following their symptom patterns and their physical and psychological performance patterns over time. I'm not sure that medical oncologists are doing that systematically, or documenting it, at all stages of the cancer.

Rather than stigmatising the physicians and the treating teams, we need to open a frank dialogue about the limits of our understanding of the true value of different treatments, for different diseases and in different clinical situations. I believe the most important thing is to offer continuous care to the patient, from the start to the end of their cancer journey – and even after the end, in supporting family and friends. I think that dividing cancer care into 'active' and 'palliative' is wrong.

In an editorial just published in the *Annals of Oncology* (23:1932–34), I discuss the importance of continuity and of supportive care, which should include the needs of terminally ill patients. We should not differentiate supportive and palliative care from active treatment. Good cancer care is a continuum, and sending the patient to a 'death home' is not ideal.



Beneficial or futile? It is often hard to predict how an individual patient will respond

SAM OGDEN/SCIENCE PHOTO LIBRARY

I agree with Matti that we should not look at palliative care as a separate system from active treatment. I also agree we should not stigmatise physicians, but instead have an open discussion about these issues. The expertise of palliative care and symptom management should be continuously integrated with tumour-directed treatment. It's about offering the correct treatment at the right time, and patients have to understand that they are part of a large team including medical and radiation oncologists, palliative care physicians, specialist nurses, community nurses and so on. As patients approach the end of their life, this team will change and the focus will be more on home care than hospital care. Oncology expertise is also needed in home care situations and within palliative care teams.

High-quality and continuing supportive care, as recommended by the European Society for Medical Oncology and other medical organisations, is definitely of primary importance. It could be that in some countries, and in some settings, oncologists are led too much by test results, rather than thinking about the real benefits to patients of offering approaches that integrate the best active treatment with the best supportive care. If that is the case, there needs to be a change. CW

In the jungle of the miracle healers

An award-winning article on the seductive powers of alternative therapists

BERNHARD ALBRECHT

It was her own fault that she lost her chance to be cured. Or was it? This article, which was first published in the German weekly news magazine *Der Spiegel,* and won its author a Best Cancer Reporter Award, explores what makes people choose alternative over conventional treatments.

It was on a Monday three and a half years ago that Renate Mulofwa* first gave in. "I can't cope any more," she said to gynaecologist Angela Kuck as she bared her breast. "I'm sure you've never seen anything as bad as this!" And she burst into tears of embarrassment.

Three days earlier the naturopath who was treating her had jumped back in alarm as blood came spurting out at him. The tumour was as large as a grapefruit and was pushing outwards as though trying to escape from her breast. It had eaten away her skin, so that Mulofwa described what remained as a "glacier landscape".

Renate Mulofwa was then 47; she had known for almost two years that she had breast cancer. Surgery was something she had never wanted. She was a woman who had always attended her mammography appointments, ever since she had first felt a hardening in her breast when she was 28. She had had her three children immunised and allowed them to be prescribed antibiotics when they were ill. She had never had anything against conventional medicine – at least not until that phone call in June 2006 that changed everything. For Renate Mulofwa, that day saw the start of an odyssey through the strange world of alternative medicine. For four years she had been pursuing that pathway, leaving it only once – briefly – in 2008.

Mulofwa had been visiting a friend when her mobile phone rang. The caller was the resident gynaecologist from the neighbouring village. He had recently arranged for a tissue sample to be taken from her left breast. She had cancer, the doctor told her curtly, and he had made an appointment for her to go into hospital the following week for surgery. At any rate, that was how she remembered it.

The gynaecologist now says that it cannot have been like that – his professional ethics would not permit him to deliver such a serious diagnosis over the phone. The truth of the matter can no longer be ascertained, but Mulofwa maintains that from the outset she found this doctor cold, uninterested and arrogant. She saw him as representing the heartlessness of conventional medicine, and then she imagined the chemotherapy


Wissenschaft

KREBS

Dschungel der Wunderheiler

Diagnose Brusttumor. Gibt es da eine Alternative zu OP und Chemotherapie? Eine Patientin aus Zürich wechselt, irregeleitet von falschen Versprechen, vier Jahre lang von einem Kurpfuscher zum anderen. Die Geschichte einer Odyssee.

Patientin Mulofwa

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DER SPIEGEL

Germany's leading news magazine.

Don't do what I did. Providing insight into why people choose alternative therapies, and what the consequences can be, helps readers avoid falling into the same traps

– the hair loss, the vomiting into the toilet. No! She decided not to give conventional medicine a look-in.

And so, regrettably, she did not find out how good her prospects were: no lymph nodes were affected, the cancer was less than five centimetres across and was 'moderately differentiated'. Chemotherapy would probably not have been needed at all, she could have been treated effectively with hormone inhibitors. Her chances of a cure were good.

'I was stubborn'

"I don't want to push the blame onto others. I was stubborn and had got it into my head that I would show everyone that there were other ways of doing it," she now says. She shakes her head, on which, after five cycles of chemotherapy, nothing but fuzz is growing. On the shelves in her small living room is a photo of her twenty years ago, with long blonde hair and a beaming smile – she is doing the splits on a tree trunk that is bridging a stream. Now she thinks that she looks more like "a newly hatched vulture".

But is it all 'her own fault'? Her fault because she let herself be seduced by the promises of the wonder doctors? To what extent are the seducers themselves to blame?

Renate Mulofwa now recognises traits in herself that make her an ideal victim of that 'alternative' parallel world. She sees herself as easily influenced, she takes decisions on the basis of gut feeling, and if a charismatic healer clasps her warmly by both hands and proclaims in a tone of complete confidence, "We can crack it!", that goes down better with her than the ruthless realism of conventional doctors.

And so she entered the jungle of alternative medicine, where no one showed her how to distinguish between genuine treatment methods and life-threatening quackery.

The first tip came from her brother – he knew of a farmer who had cured a colleague of a persistent allergy through laying on of hands. Mulofwa drove in her green Volkswagen camper to the Allgäu in southern Germany. A friendly elderly man with a red face and a large stomach welcomed her into his living room. In the corner stood an altar, surrounded by statues of Mary of every conceivable size. His hands on her shoulders were warm; it felt good to feel the energy flowing. And the farmer was modest; he made no mention of payment. Mulofwa gave him €100. She stayed a week, sleeping in the camper van and enjoying the outdoors and her freedom.

Once she met another cancer patient

She saw him as representing the heartlessness of conventional medicine

Could she have abandoned her approach at this point, brought down to earth by this failure?

there, who secretly advised her, "I've had surgery and chemo as well – you should do the same! Just don't say anything to him about it; he doesn't like it." Mulofwa learned that with healers it's just like with doctors: if you want them to try to help you, you have to do what they say.

A small book with a yellow cover revealed the next step to her. Published in 1978, it still ranks among Amazon's top 10 cancer guides. Under the title *Advice for the Prevention and Natural Treatment of Cancer, Leukemia and Other Seemingly Incurable Diseases,* the author – also a farmer – leads people to believe that cancer can be 'starved out' by a 42-day diet: a widespread misconception that flies in the face of all the insights of cell biology. The theory is preceded by numerous accounts of cancer patients who have allegedly been cured by the 'Bruess diet' – even without surgery.

Mulofwa stuck rigorously to the diet: for six weeks she had nothing but tea and fruit juice, with thin onion soup at lunch time. She lost 14 kilos, her hair fell out in clumps, but the lumps in her breast got no smaller.

A chance for a rethink

Could she have abandoned her approach at this point, brought down to earth by this failure? "My mother is very strong. You can talk to her, but in the end she does what she wants," says her daughter, a qualified nurse with experience of working on cancer wards. Since she represents conventional medicine, she says, her mother would not have followed her advice in any case.

Vera Hermann, her alternative therapist and friend, also avoided conflict. At first, choosing her words carefully, she tried to encourage Mulofwa to have surgery – after all, the alternative route was still an option after that. "But you were wearing blinkers; you only took in things that fitted with your world view," she now says, and Mulofwa ruefully acknowledges, "You're right. If you had spoken to me forcefully like other people did, I would have stopped coming to you!"

By this time Mulofwa had already accumulated two shelves of books about her cancer. What all of them have in common is that they accuse conventional medicine of only treating the symptoms, not the cause, and they suggest an apparently simple way out of the problem. Sometimes the solution is large doses of vitamins, sometimes information about the healing properties of Aloe vera that has supposedly been suppressed by scientists, sometimes you simply have to work on your relationship with your mother. Under seductive titles such as *Chemotherapy Heals Cancer and the World is Flat* (another longstanding bestseller), authors of dubious standing skilfully attack conventional medicine at its weakest point.

In a book about Germanic New Medicine, written by the former German doctor Ryke Geerd Hamer, who has been charged and convicted on a number of occasions, Mulofwa read about the 'iron rule of cancer', according to which tumours are the result of psychological conflicts. With a purple highlighter she marked the passages stating that conventional doctors put cancer patients in a panic. "Knowing patients" have no fear because they know that metastases do not exist.

Vindicated?

Mulofwa saw herself vindicated. Was it not this very panic that was paralysing her? She therefore avoided all conventional medical advice or newspaper articles and turned off the television as soon as a talk show mentioned her illness. In her books, on the other hand, Mulofwa learned that she herself was responsible for her cancer. Had she not left her two faithful ex-husbands, one after the other, after many years of happy marriage, in order to eventually marry a younger African man in 2003? "Although many people didn't understand me then, it was deep love at first sight, and now he stands faithfully by me," says Mulofwa. But she believed that the cancer was a punishment for what she had done.

She chased tirelessly from healer to healer. She had her bowel cleansed of toxic waste, was injected with mistletoe extract and tried out dubious procedures such as snake venom therapy and autohaemotherapy. She took part in the mass healings of a Nigerian priest who worked himself up into a frenzy on the stage, and in Tibetan group yoga events.

Today some of these experiences bring tears of laughter to her eyes. One alternative practitioner pushed her in the back, to test her aura. She then heard him rummaging in a toolbox and doing something behind her. A "repair to the aura", carried out with hammer and screwdriver, he explained. "Obviously I thought, 'this is pure humbug' – part of me isn't stupid. But I also

thought, 'it won't do any harm.'"

At the start of 2008, in the months before her capitulation, she believed that she was in the best possible hands with the general practitioner Dr Norbert Vogel. The imposing practice with bright rooms, now managed by a successor, lies in an exclusive quarter of Zurich, opposite a hospice for the terminally ill. Mulofwa remembers Dr Vogel as a small man in his late 50s, in old-fashioned pleated trousers, who kept talking about Jesus Christ.

By then her breast cancer had already grown considerably. She was having to stuff more and more tissues into the bra cup of her right, healthy breast to stop people noticing anything. The tumour secreted a yellowish discharge, and it bled.

Dr Vogel had promised her great things from the miracle product amygdalin – an extract of apricot kernels that alternative practitioners also refer to as Vitamin B17. She had read that scientists and the pharmaceutical industry were conspiring to suppress information about the effectiveness of this substance, because it could not be patented. Mulofwa had paid out 4000 Swiss francs in cash for her daily injections of the wonder drug. Vogel, who has since emigrated to South America, leaving only an email address, did not respond to an enquiry from *Der Spiegel*.

The doctor's handwritten notes from that time consist of one page of spidery writing. On 18.4.2008 he noted, "exulc. tumour significantly grown bleeding" – on this very day he had seen the bleeding breast and Mulofwa had begged him to refer her after all to a hospital. "I had such a bad conscience – after all, he had tried so hard to help me," she said.

Alternative therapies. You must do as you are told

Yet the results of the monthly blood tests filed away by the doctor show that under his care she was becoming steadily more anaemic – to an extent that was potentially life-threatening. Three days later, when Angela Kuck admitted Mulofwa to the Paracelsus Clinic in the Swiss town of Richterswil, the gynaecologist assessed the patient as too ill to be operated on, at that stage, on account of her poor blood values. She was given blood transfusions, and the hospital chaplain heard her confession.

It took three days for Mulofwa's condition to improve enough for the operation to be carried out. The medical report states that five out of eleven lymph nodes in her armpit were affected at this time, and the cancer had spread to her pectoral muscles.

The patient next to Mulofwa in the three-bed room was Barbara. Barbara was the same age, had colorectal cancer, and like Mulofwa had not wanted to have surgery. In conversation, the two kindred spirits discovered that they had been treated by the same healers. Mulofwa recovered quickly from her operation, but her new friend was soon writhing with the pain of her tumours. The nurse moved her to an adjacent room. The following night Mulofwa heard her screaming, and in the morning she was dead.

That evening, with tears streaming down her face, she sat beside Barbara in the basement, where the corpse, surrounded by flowers, was laid out – in line with the usual anthroposophical practice in the clinic. Mulofwa was shocked. She resolved to accept whatever the doctors

BLICKWINKEL/MCPHOTOS, HEIKO WOLFRAUM, ALAMY, MANFRED RUCKSZIO

"Obviously I thought, 'this is pure humbug' – part of me isn't stupid. But I also thought, 'it won't do any harm'"

offered her: radiotherapy, hormone blockade with tablets, three-monthly slow-release injections. Chemotherapy was the one thing that she still refused.

Over the following months Mulofwa gained strength for a new life. After nine months she felt well and stopped taking the hormone inhibitors – which she should have taken for five years. Then, more than a year after the operation, a lump appeared for the first time in the other breast. The doctor who examined her ordered a full-body PET scan.

Too late for a cure

The tomography image shows her whole body scattered with dots. These are metastases – in the bones, the lymph system, the liver and the lungs. They are not curable, the doctor told her, but palliative chemotherapy might keep them in check for a few months or years.

Weeping, Mulofwa confided in her sister-in-law. She knew what to do: an alternative therapist in Zurich – a friend had given a glowing report of him. There it was again, the temptation. Before long, Mulofwa was once more having coffee enemas, soaking in alkaline mineral baths and swallowing a handful of herbal capsules every day.

Mulofwa could feel her strength dwindling. Her weight was falling day by day. "Everyone dies sometime," she said to her friends. Her youngest son and her daughter no longer needed her; they would make their own way in the world. Her husband would probably go back to Gambia. She was grateful to him; he had been just right for her during those years. The illness didn't spell the end of their physical relationship. Her husband had told her that for Africans the breast was not sexy – its job was to suckle babies.

Mulofwa's concern, though, was her elder son, who still lived with her. She had never spoken to him about her illness, but she knew that he was suffering. More or less on the day of her cancer operation he had given up his job at an electrical superstore; since then he had barely got himself together at all. For him, she thought, she must hang on.

Her dry cough was becoming obstrusive, but the worst thing was her shortage of breath. Mulofwa felt as though her lungs were wedged into her ribcage. This time her alternative therapist sent her to "a doctor that he trusted": Joachim Chrubasik, a man with the impressive title of "Prof Dr med" attached to his name.

Reassured by a title

For a second time the doctor title instilled in Mulofwa a sense of security. She believed that Chrubasik combined conventional and complementary approaches. Now she says, "He was the very person who once again brought me to the brink of death."

Until 1996 Chrubasik was an anaesthetist in charge of a pain clinic in Heidelberg – a prominent researcher with a long list of publications to his credit. Yet previous colleagues recall that, even then, he was allegedly manipulating his patients and using questionable treatment methods. Then on account of irregularities he was stripped of his official status. His boss at that time, Eike Martin, comments, "I was glad that the problem was solved in this way, because with his obsessiveness and his exaggerated opinion of himself Chrubasik had repeatedly put patients at risk."

Chrubasik peddles himself and his work at alternative 'mind body spirit' events. The booklets available on his stand at the 'First experience fair', held near Zurich, sported titles such as *The Creation of the World* and *Cosmopsychobiology*. According to his business partner, Chrubasik has often cured cancer patients at an advanced stage of the disease.

The professor is a sturdy, pink-faced man with artistically styled grey hair and a beard. At the fair he denounces the pharmaceutical industry and in the next breath talks about how after 50 years he no longer needs glasses because he regularly takes rosehip powder. While he is speaking, pill boxes and juices are being circulated among the audience; many of them bear the words "based on Prof Chrubasik" as part of the product name, while others come from a pharmaceutical company that uses his address.

Mulofwa is familiar with many of these products. She says that Chrubasik gave her two large bagfulls that he had packed in the back room of a Zurich pharmacy.

Looking back, says Mulofwa, she fell for the professor's charisma in an instant. He prescribed gel-padded shoes and herbal painkillers for her hip pain (which was caused by the metastases). Today he explains his strategy: "The most important thing is to get cancer patients free of pain. Then they live longer." When she told him about her coughing and shortage of breath, he listened to her chest and said her lungs were clear. Even now he emphasises, "Her lungs were always good."

"With his obsessiveness and exaggerated opinion of himself he had repeatedly put patients at risk"

"My life has been saved twice, and both times it was conventional medicine that did it"

The turning point

Miklos Pless, who treated her shortly afterwards, remembers things quite differently. At that time Mulofwa's condition was life-threatening, the oncologist says. As a result of the cancer, large quantities of water had accumulated in her chest and her lungs could no longer cope with the resistance they encountered. Mulofwa nevertheless believed Chrubasik. It was not until she was at home and her son broke his silence that her conviction began to waver. Weeping, he begged her, "Please, Mum, have the chemo!" That was the turning point. In a flash I realised what I had done to my life with my obstinacy.

Pless, the oncologist, had prepared himself well for his first consultation with his new patient. From the alternative therapist he had already learned that Mulofwa had until then always rejected conventional medicine. The majority of patients, he says, are afraid that in hospital they will be drawn into a spiral in which one treatment invariably leads to another. And this anxiety is not unjustified, in Pless's view. "I therefore promise my patients that I shall always respect their autonomy," he says.

He knows little about complementary medicine, he admits, but he recommends therapists whom he trusts if that's what patients want. The fact that he was not in principle hostile to alternatives was what won Mulofwa over.

The records show that Pless was expecting an emaciated woman who would probably be in a wheelchair. So he was surprised to see her walk into his admission room. He didn't say, "How could you let it come to this?" He didn't say, "You are incurably ill." Instead his words were: "Your general state is still very good. If you give yourself a chance, you could soon be feeling much better."

He first sent Mulofwa to a lung specialist, who spent several sessions puncturing her life-threatening effusion. Then Mulofwa said 'yes' to chemotherapy. The results astounded even Pless: the tumours shrank, the pain disappeared, Mulofwa could breathe freely again, although the cough remained. Three months later the lung specialist reported with surprise how well her lungs were functioning.

Mulofwa receiving chemotherapy. "I was stubborn"

A second life

In January 2011 Mulofwa celebrated her 50th birthday and, as the invitation put it, her 'second life'. Today, a year later, she has five cycles of chemotherapy behind her. Apart from the hair loss she has had no major problems, she says. "No vomiting, no nausea, each time I just feel a bit weaker than usual for two days."

She seems stronger than she did then, says Hermann, the alternative therapist who is still at her side. She is one of three complementary therapists whom Mulofwa still trusts. Her clear verdict is, "My life has been saved twice, and both times it was conventional medicine that did it," and she deliberately courts publicity: "I want to spare other women what I have been through."

Mulofwa still hopes that she can beat the cancer, with the help of her self-healing powers, with globules, herbs – and chemotherapy. CW

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* The patient's name has been changed.
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How bad news can be good news for cancer services

PETER McINTYRE

Knowing what needs to be done is one thing. Making it happen is quite another. Well-informed media stories that highlight shortcomings and failings can help focus minds on the need for urgent action.

The media plays a critical role in creating political momentum for change to improve health services, according to the UK's National Cancer Director, Mike Richards. He speaks from personal experience, as it was a combination of evidence-based statistics and human interest stories that, in 1999, triggered the then Prime Minister Tony Blair to appoint him as what the media quickly dubbed 'the Cancer Czar'.

Richards would prefer not to be in the public eye, but says that media attention is essential if things are going to change. "My appointment was greeted as good news for about 24 hours and after that all the bad news stories came out about people not getting treatment and about late diagnosis. We were deluged with bad news and I got experience very quickly in dealing with the media.

"Let me be honest, I have ambivalent feelings towards the media. I measure my success by how rarely I have to do the [BBC Radio] *Today* programme. I don't need the publicity – I am not trying to get elected. But I know that we need those bad news stories. If all the journalists stopped criticising and said cancer is wonderful, my ability to move things would be diminished."

Richards was speaking to broadcasting and print journalists at an 'Off the Record' training course, 'Can Europe cope with the rising burden of cancer?' organised by the European School of Oncology (ESO) and the European Broadcasting Union (EBU) on June 18 and 19.

The EBU has a record of high-quality media briefings for broadcasters in Europe, but this was the first time that they had tackled a critical health issue such as cancer. ESO, which provided the expertise and content for the training event, has organised a number of initiatives to bring together cancer specialists and journalists in various settings and parts of the world, but this was the first time it had focused on broadcast journalists. The event was organised as part of ESO's contribution to the European Partnership for Action Against Cancer. It was co-financed by the EU Health Programme and was held in conjunction with the Partnership's Second Open Forum, which was hosted by Italy, and held in the Ministry of Health in Rome.

CRISTINA NICHITUS

DALILA DULGHERIU

A bone marrow registry for Romania. The power of good reporting to galvanise demand for action was demonstrated by Pro TV's Paula Herlo, pictured here at the Ministry of Health in Bucharest, giving a sample of her blood to join the bone marrow registry that was set up following her series of hard-hitting reports. *Below:* Paula with a young leukaemia patient who appeared in one of her reports. The full story can be found in *Cancer World* Jan–Feb 2011

ESO's primary focus is on giving doctors and other health professionals access to the knowledge that they need to give patients the best possible treatment and care. But Kathy Redmond, editor of ESO's magazine *Cancer World*, sees working with journalists as a significant part of the ESO brief to educate and explain the complexities of cancer and to improve public understanding of the disease. "There needs to be much more engagement between the cancer community and the mass media. There is a disconnect between what the media usually highlights and what people need to know. Whether it means to or not, the media shapes public attitudes, beliefs and knowledge about cancer and has a responsibility to ensure that what it writes or broadcasts is correct."

The journalists who attended the event in Rome came from broadcasting organisations and from print and on-line outlets, and they were looking for ways to make their reporting more effective. Many felt there is often a lack of accessible data to give a solid basis for reports on issues such as screening, early diagnosis and treatment.

Tetyana Melnychenko, a reporter and presenter for Ukraine National Television said, "I understand we need to be a bridge between the patient and the policy makers. I would like better statistics to be available in the Ukraine, particularly about survival."

Also present were journalists from the Czech Republic, Bulgaria, Estonia, Romania, Spain, Greece, Portugal, the UK, France, Denmark, Latvia, Lithuania, Poland, Slovenia, and Sweden. This list includes many of the countries where health services are being squeezed by austerity measures, and this was clearly an issue for the journalists and the experts. "If I had to choose a word I would remember this course by, it would be 'money'," said Jasmina Jamnik, from RTV Slovenia. "Money is a problem everywhere. But this age of austerity could be a chance for prevention."

Who is listening?

Money was not the only constraint. Claudia Laslo from Radio Romania pointed out that her country had had 30 different Ministers of Health over the

"I understand we need to be a bridge between the patient and the policy makers"

A PARTNERSHIP FOR ACTION

- EPAAC is a European Union initiative set up in 2009 to enable member states to work in partnership with one another and with professional, charitable, campaign and advocacy organisations involved in the anti-cancer effort.
- It aims to close the gaps between the best and the worst performers across Europe by cutting down on the duplication of effort and promoting transfer of knowledge and best practice.
- The partnership pursues a variety of initiatives in prevention, early detection, treatment and care, research, data and information, and cancer plans.
- The Off the Record ESO/EBU journalists training course, 'Can Europe cope with the rising burden of cancer?' formed part of the Partnership's action to communicate with a wider audience, and took place at the second EPAAC Open Forum, held in Rome, June 2012.
- The third and final Open Forum will be held in Brdo pri Kranju, Slovenia, in November 2013. The initial phase of EPAAC will come to an end in February 2014.

past 20 years and it was hard to get politicians to listen.

Richards urged her not to give up. "You would be surprised at how many do listen to your stories. I think we have a major problem of changing perspectives and beliefs. You can influence the political system. It takes time. It took time in the UK. Unless the politicians are presented with a problem, they will leave it alone. They have lots of other demands on their time and on resources."

He said that the UK had been in denial about the poor state of cancer services, despite the mortality figures for the UK being worse than other western European countries. Even when the first EUROCARE statistics showed mortality rates lagging behind "we dismissed them as unreliable and the doctors said they cannot be true."

Things began to change as cancer experts, cancer charities and patient groups became concerned. "Who was listening? Very importantly the media was listening and I am sure you all know the power of the individual story backed up by statistics.

"What influenced Tony Blair over a period of three, four or five years was you, the journalists, writing stories. The bad news was there and you could not ignore it and journalism had a big part to play."

The UK has improved its record on cancer, although it is still behind the leading countries. "What changed is that it became a political issue," Richards said. "Perhaps the single most important thing is building the community that says we must have better survival or outcomes for cancer. We need to get clinicians, academics, managers, civil servants, patients, politicians and charities pulling together."

Tit Albreht, from the Slovenian Institute of Public Health, led a working group to survey national cancer plans across Europe, to be published later this year. He said that the media had a role to play in removing an aura of shame that exists in some countries around cancer.

In Slovenia the media had helped to raise the response rate for colorectal cancer screening from 28% to 71%, so that it is now amongst the best in Europe. In all about 800 stories had been written, and he recalled one about a man who had delayed sending in his stool sample, but had then spoken out after screening discovered cancerous polyps, which were then removed.

Albreht responded positively to a suggestion from Olaf Steenfadt, the EBU project manager who chaired the sessions, that media strategies should be included in national cancer plans. "We will definitely work on it," he said. "It is not part of the current template, but it is extremely important."

Journalists received briefings from cancer experts about the latest statistics and discussed ways in which they can broadcast and write more clearly about cancer prevention, screening, treatment and the social issues that surround cancer. Silvia Francisci from the Istituto Superiore di Sanità, the leading scientific public health body in Italy, showed journalists how statistics available on the internet could be used to compare outcomes and value for money across Europe. Elke van Hoof, head of the

Journalists saw how statistics available on the internet can be used to compare outcomes across Europe

Belgian Cancer Centre, talked about the strengths and weaknesses of screening programmes for cancer.

A hard-hitting panel discussion included Cora Sternberg, head of medical oncology at the San Camillo-Forlanini hospital in Rome and Jaimie Brown, head of communications for Novartis Oncology in Europe. And although the journalists pulled no punches in quizzing Jaimie Brown about the pricing policies of drug companies, they were delighted to have someone from the industry there. Mette Weber, who writes for the Danish Cancer Society, remarked "Excellent that you invited a rep from the pharma industry was well. A nice balance of perspectives!"

New approaches, new perspectives

It was clear from feedback at the end of the course that many of these journalists will increasingly link their stories on individual cases to statistical data and will have a greater awareness of the balance of risks and benefits in issues such as screening. There was also increased interest in focusing on cancer survivors. Silja Paavle, a reporter on the Estonian newspaper SL Õhtuleht, said, "Nobody in Estonia has written about rehabilitation and I think I need to do this."

Maya Dancheva, the health reporter at Bulgarian National Radio, felt she was now better equipped to use statistics for comparative analysis of the cancer picture in Bulgaria with other European countries.

Meelis Süld, a producer and reporter on Estonian Public Broadcasting, said he would ask more critical questions about how patients can get the best treatment, but that it was also important not to make cancer a scary subject. "I will try to focus more on the patients, not to scare them away, because people are scared about illness."

For Olaf Steenfadt, such training courses are part of the EBU and public service broadcasting commitment to quality journalism in difficult times. "Fewer resources and cuts on the one hand and more complex and interrelated topics on the other challenge each editor, journalist and correspondent. An in-depth understanding of the main issues, such as the rising burden of cancer, can promote safer news judgement and contextualisation for the benefit of large mass media audiences.

"The professional exchanges between mainstream news journalists and specialist science writers proved extremely useful for both sides. While producing content for different target groups, they shared the common task of identifying trends and finding new angles to report on cancer."

Using the experience gained in its media training work over the past years, in 2013 ESO will produce a journalists' guide to reporting on cancer. Anna Wagstaff, assistant editor of *Cancer World*, who has led much of this work, says that journalists want to be able to put their stories into context, and to have a greater understanding of what really makes a difference in treatment and care. "Many journalists say they are tired of doing endless stories about individual patients who cannot get the treatment they need, and of being told that the problem is lack of money. Some broadcasters even involve their journalists in fund-raising initiatives, but that is not what journalism is about. Journalists want to be in a position to help the public understand cancer, and they want the information and insight to help them ask the right questions of policy makers about shortcomings in cancer services and how these can be addressed. When journalists do their job well, patients are more likely to get the treatment and care they need." CW

PROMOTING QUALITY COVERAGE OF CANCER

Off the Record journalists' course, Rome 2012

ALEXANDRA ZAMPETTI

- In addition to the training course in Rome, ESO has provided courses on cancer reporting to journalists in Cairo and Damascus, and at the two most recent gatherings of the World Conference of Science Journalists.
- ESO's media team has worked with EUROCHIP to provide training to professionals involved in cancer screening and cancer registries.
- ESO has run an annual Best Cancer Reporter Award since 2006. A total of 22 journalists from 10 countries have received awards so far. Their winning articles can be read at CancerWorld.net (go to the Media menu)

impact factor

nature REVIEWS CLINICAL ONCOLOGY

For localised prostate cancer, does technology equal progress?

MATTHEW R COOPERBERG

Recent evolution of prostate cancer treatment reflects technological arms races driven by economic incentives rather than high-quality evidence – as exemplified by proton-beam radiation, recently found markedly inferior to far less expensive alternatives. Another study found promise for focal treatment, but much research is required before this could become a standard option.

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Efforts are constantly ongoing to introduce alternatives to standard treatments for localised prostate cancer that offer equivalent or better oncological efficacy, together with reduced side-effects. However, the recent history of treatment evolution has been driven more by marketing hype and misaligned financial incentives than by high-quality evidence. Two studies have generated a great deal of attention in the media, and are illustrative of broader ongoing trends in the field. The first study, by Sheets et al.,[1] analysed data from the Surveillance, Epidemiology, and End Results (SEER) Medicare-linked database to compare proton-beam treatment with other forms of external-beam radiation therapy (EBRT) – namely intensity-modulated radiation therapy (IMRT) and conventional conformal radiation – between 2002 and 2006, using both standard multivariable analysis and propensity weighting.

The growth of IMRT has been absolutely explosive: from 0.15% of EBRT cases in 2000 to 95.9% in 2008.[1] Overall, compared with conformal radiation, IMRT was associated with statistically significant, but modest clinical benefits: 9% less gastrointestinal toxicity (only on the propensity-adjusted analysis) and fewer hip fractures (which were uncommon in all groups), but no difference in urinary outcomes and 12% more erectile dysfunction. Proton-beam treatment was associated with no benefits compared to IMRT – and in fact caused 50% greater bowel toxicity, even after propensity adjustment. Proton-beam treatment was also marked by trends towards greater erectile dysfunction.[1]

The debate about proton-based versus photon-based radiation recalls similar discussions about robot-assisted versus open prostatectomy; the discussion section of the present study[1] in fact draws an explicit parallel to an earlier Medicare study focusing on this question.[2] Indeed, there are similarities in the way these technologies have been developed and marketed.[3] Both Medicare analyses are also marked by limitations in their use of administrative billing codes as proxies for quality-of-life outcomes, which ideally should be assessed via validated patient-reported questionnaires. However, important differences should be noted. The prostatectomy paper

analysed robot-assisted surgery data from many surgeons, mostly lower-volume providers early in their learning curves.[2] The proton-beam experience, conversely, was dominated by a single centre in southern California, which is an experienced, high-volume (and aggressively marketed) centre for proton-based prostate treatment; this concentrated experience should, if anything, represent a best-case for outcomes. Also, unlike the case of proton-beam treatment, many other studies have found clear benefits for robot-assisted prostatectomy compared with open prostatectomy.[4]

Furthermore, the capital and marginal costs of robot-assisted versus open surgery are utterly dwarfed by those of proton-based versus photon-based radiation. The additional costs of robotics are absorbed by hospitals, whereas the costs of novel radiation technologies are borne directly by Medicare and other payers. Costs were not directly addressed in the Sheets et al.[1] paper; however, another recent Medicare study found IMRT to be roughly 50% more expensive than 3D conformal radiotherapy, and about twice as expensive as brachytherapy or surgery (whether open or minimally invasive).[5] Proton-beam therapy is twice as expensive again as IMRT. A decision analysis demonstrated in 2007 that even if decreased morbidity allowed dose escalation up to 90 Gy, proton-beam treatment still would not be cost effective.[6]

At this point, it seems very unlikely that proton-based therapy will allow such dose escalation. Indeed, while there are theoretical radiation biological advantages to proton-beam therapy, no clinical study – anywhere, ever – has shown any clinical advantage in terms of either oncological or quality-of-life outcomes. Proton-beam prostate treatment fortunately remains uncommon, but new facilities are proliferating rapidly, and because once a facility is constructed there is a major incentive to recoup a prodigious investment, local prostate cancer practice patterns tend to shift to reflect more use of proton-beam treatment.[7]

The other recent paper, from Ahmed et al.,[8] reported MRI-guided focal treatment with high-intensity focused ultrasound (HIFU). HIFU has been the subject of multiple series, mostly in Europe. The results have been decidedly mixed, with some series reporting excellent outcomes, and others finding low rates of cancer control, high rates of retreatment, and mediocre quality of life.[9] Given this ongoing uncertainty, the technology remains investigational in the USA.

> "No clinical study – anywhere, ever – has shown any clinical advantage for proton-beam therapy"

Ahmed et al.[8] reported on 42 men with low-risk to intermediate-risk prostate cancer treated with HIFU targeting areas of cancer based on biopsy and imaging. The protocol allowed up to 60% ablation of the prostate, and required transperineal template prostate biopsies under anaesthesia before and after therapy. At 12-month follow up, quality-of-life outcomes were generally good, although there were certainly impacts on sexual and urinary function, particularly in the short term, and in some cases in the long term. Twenty-three per cent of the patients had follow-up biopsies positive for cancer, and 10% were retreated. Follow up was not sufficient for assessment of long-term oncological efficacy.

What is novel about this study[8] is not HIFU *per se*, but rather its use in a relatively well-constructed, prospective study of focal therapy. Indeed, for focal prostate cancer treatment, the ablative technology is almost irrelevant. If prostate cancer can be identified reliably, it can be destroyed by any number of modalities: HIFU, cryotherapy, interstitial laser therapy, photodynamic treatment, focal radiation and so on. Although the results might be considered promising, many questions remain regarding patient selection, workup, imaging, and follow up, which must be answered before focal treatment could be considered for routine clinical practice. Because HIFU is not broadly available, direct cost comparisons to other treatments are not possible, although the imaging and pathology costs for an MRI-based focal protocol with before-and-after transperineal biopsies are likely to be significant.

Where do these studies leave us? Regarding proton-beam treatment the answer should be clear: at a time of increasingly constrained resources, it is completely unconscionable that we should continue to pay exorbitant premiums for a technology that has not been proven better, and may well be less effective, than competing alternatives. Proton-beam treatment should continue to be studied, but payment incentives must be revised – for both proton-beam treatment and IMRT – to

Key point

Proton-beam therapy for prostate cancer costs two to four times as much as standard alternatives, and in a recent study has been shown to yield inferior quality-of-life outcomes. Focal therapy may eventually offer a favourable alternative, but much research is needed on patient selection, workup, follow up, and outcomes assessment.

provide reimbursement per patient, not per fraction, and neither should be reimbursed so richly compared to surgery or brachytherapy.

More generally, strident champions of expensive technology without supporting evidence run the risk of winning short-term, pyrrhic victories, but losing the overall war: avoidable cost and morbidity associated with overtreatment of prostate cancer is a major driver behind calls to end prostate cancer screening. Focal therapy remains an intriguing alternative, but requires much more study – and the fact remains that for most men with low-risk prostate cancer, the best treatment is active surveillance rather than any local treatment.[10]

Ultimately, what is needed in 2012 for localised prostate cancer is not new technologies, but rather new paradigms for routine, standardised assessment and reporting of both oncological and patient-centred outcomes; for risk stratification of tumours and targeting intensity of treatment to individuals' oncological risk and comorbidity; and for full engagement of patients in shared decision-making based on high-quality data on both effectiveness and cost-effectiveness of treatment alternatives.

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Author affiliations

Matthew Cooperberg, Department of Urology, UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, California

Gemtuzumab ozogamicin in acute myeloid leukaemia

FARHAD RAVANDI & HAGOP KANTARJIAN

Gemtuzumab ozogamicin was withdrawn from the market after being evaluated in combination with chemotherapy in the frontline treatment of patients aged 18 to 60 years with acute myeloid leukaemia (AML). More-recent randomised trials demonstrate that low doses of gemtuzumab added to cytarabine and anthracycline-based chemotherapy benefit patients with better-risk AML.

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Treatment of patients with acute myeloid leukaemia (AML) has not changed significantly since studies in the 1980s established cytarabine and anthracyclines as the most effective agents in this disease. Several randomised trials have demonstrated that the doses of cytarabine and anthracyclines are important in specific subsets of patients. A meta-analysis of trials comparing high-dose with standard-dose cytarabine during induction has shown an improved relapse-free and four-year overall survival for patients younger than 60 years with *de novo* AML who receive high-dose cytarabine as a part of their induction regimen.[1] This finding was further corroborated by a recent randomised trial demonstrating a higher response rate and improved overall survival in patients younger than 46 years who received high-dose cytarabine induction compared with those receiving the standard cytarabine dose (six-year overall survival 52% vs 43%; P=0.009).[2] Other data have suggested that further escalation of the cytarabine dose beyond levels that saturate intracellular arabinofuranosylcytosine triphosphate is not beneficial.[3]

Cytarabine dose is particularly important in the treatment of patients with the core-binding factor leukaemias, which have a more favourable risk profile; the administration of several

courses of high-dose cytarabine as consolidation therapy improves the survival of these patients.[4] In addition, a higher dose of the anthracycline daunorubicin (90 mg/m^2 vs 45 mg/m^2) benefits patients younger than 60 years, with the exception of those with adverse cytogenetics and molecular aberrations (such as FLT3 internal tandem duplication).[5]

Clearly, escalation of chemotherapy dose seems to benefit patients with more favourable risk disease including young patients and those with more favourable cellular biology determined by cytogenetics or molecular abnormalities. It is tempting to speculate that the leukaemic cells in these patients are more susceptible to the effects of cytotoxic chemotherapy because of as yet unidentified mechanisms. Therefore, the limiting factor in such patients will be the limits of tolerability of the escalated dose of chemotherapy. Other agents with novel mechanisms of action and with non-overlapping toxicity can potentially further improve the outcome when added to the intensified standard regimens. These potentially include cladribine, clofarabine, FLT3 kinase inhibitors and gemtuzumab.

A recent study by Castaigne and colleagues[6] is among several important randomised trials evaluating the benefit of a low dose of gemtuzumab added to the back-bone of cytarabine and anthracycline-based induction chemotherapy. In this trial, 280 patients with newly diagnosed AML aged between 50 and 70 years were randomly assigned to receive cytarabine 200 mg/m^2 as a continuous infusion for seven days and daunorubicin 60 mg/m^2 daily for three days with or without a fractionated course of gemtuzumab 3 mg/m^2 on days 1, 4 and 7.[6]

There was a significant overall and event-free survival advantage for the patients treated with gemtuzumab. At two years, event-free survival was 41.4% versus 15.6% in patients treated or not treated with gemtuzumab, respectively, translating to an overall survival advantage for patients who received gemtuzumab (median 25.4 months vs 15.3 months). This benefit was mainly seen in patients in the better-risk groups based on baseline cytogenetic assessment.

In the SWOG 106 study, patients between the ages of 18 and 60 years with AML were randomly assigned to receive chemotherapy with or without gemtuzumab 6 mg/m^2, and although there was no overall survival benefit, patients with favourable-risk cytogenetics who received gemtuzumab had an improved overall survival.[7] It is important to note that patients who received gemtuzumab were treated with a lower dose of daunorubicin (45 mg/m^2 for three days, now considered inferior) compared with 60 mg/m^2 for three days for patients not receiving gemtuzumab, with the intent of providing 'equitoxic' regimens.

> "Low doses of gemtuzumab are able to increase the intensity of induction therapy without increasing its toxicity"

Burnett and colleagues have reported that the addition of a low dose of gemtuzumab (3 mg/m^2) to standard AML chemotherapy regimens was associated with a significant improvement in overall survival in younger (mainly ≤60 years) patients with favourable-risk and intermediate-risk AML.[8] Furthermore, Delaunay and colleagues reported that the addition of a low dose of gemtuzumab (6 mg/m^2) to chemotherapy significantly benefits younger patients (between 18 and 60 years) who did not receive an allogeneic stem-cell transplant on first remission (event-free survival advantage for patients who received gemtuzumab P=0.045).[9] A more recent study reported by Burnett and colleagues came to the same conclusion as the previous trial, again demonstrating a benefit for intermediate-risk and favourable-risk cytogenetic groups among the older patients (between 51 and 84 years) who received chemotherapy plus gemtuzumab compared to those receiving chemotherapy alone (three-year overall survival 25% vs 20% for those treated with versus without gemtuzumab, P=0.05).[10]

With the exception of the SWOG 106 trial, where the addition of gemtuzumab was associated with a significant increase in induction mortality (5.8% vs 0.8%, although these data have not been well scrutinised), in all other reported studies, gemtuzumab was not associated with a significant increase in morbidity and mortality. In particular, and perhaps because of the low doses of gemtuzumab employed in all trials, the incidence of sinusoidal obstructive syndrome of the liver was low. Therefore, low doses of gemtuzumab are able to increase the intensity of induction therapy without increasing its toxicity and, in doing so, benefit the more-favourable-risk population of patients with AML. This benefit in patients with more favourable risk is as would be expected

Key point

The addition of a low dose of gemtuzumab ozogamicin to cytarabine and anthracycline-based induction and consolidation chemotherapy improves survival in patients with more-favourable-risk acute myeloid leukaemia.

according to the arguments for the susceptibility of this population to dose intensification.

The trial by Castaigne and colleagues,[6] corroborated by data from several other randomised trials, clearly establishes gemtuzumab as an important drug for patients with better-risk AML. Why gemtuzumab is effective in this specific subset of patients requires further preclinical, translational and clinical studies. Its high efficacy in treating acute promyelocytic leukaemia (APL) is well established and may be related to the higher expression of the target molecule, CD33, in APL cells. Pending these studies, however, the benefits of gemtuzumab should not be withheld from the appropriate patients (including those with APL). Progress in AML has been slow. We clearly need to accept positive data produced and confirmed by several randomised trials.

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Author affiliations

Farhad Ravandi and Hagop Kantarjian, Department of Leukemia, University of Texas MD Anderson Cancer Center, Houston, Texas

newsround

Selected reports edited by Janet Fricker

Preoperative chemoradiotherapy improves survival in oesophageal cancer

■ New England Journal of Medicine

Preoperative chemoradiotherapy improves survival among patients with potentially curable oesophageal or oesophagogastric-junction cancers, a phase III Dutch study has found.

Oesophageal cancer, which is the eighth most common cancer worldwide, is responsible for more than 400,000 deaths a year, with five-year survival rates rarely exceeding 40%.

For several decades the role of neoadjuvant chemoradiotherapy has been debated. "In most randomized trials, no survival benefit could be shown, and the trials were criticized for inadequate trial design, samples that were too small, and poor outcomes in the surgery-alone group," write the authors of the current study. While meta-analyses have suggested survival benefits from neoadjuvant chemoradiotherapy, this has been at the cost of increased postoperative morbidity and mortality.

In the current study, between March 2004 and December 2008 Ate van der Gaast and colleagues, from Erasmus University Medical Centre, Rotterdam, randomly assigned 368 patients with resectable tumours (75% had adenocarcinoma, 23% squamous-cell carcinoma, and 2% large-cell undifferentiated carcinomas) to receive chemoradiotherapy followed by surgery (n=178) or surgery alone (n=188). The chemoradiotherapy regimen consisted of weekly administration of carboplatin (doses titrated to achieve an area under the curve of 2 mg/ml per minute) and paclitaxel (50 mg/m² of body-surface area) for five weeks and concurrent radiotherapy (41.4 Gy in 23 fractions, five days per week).

Results show that the median overall survival was 49.4 months in the chemoradiotherapy plus surgery group versus 24 months in the surgery-alone group (HR 0.66; P=0.003). At one year, overall survival was 82% for the chemoradiotherapy plus surgery group, versus 70% in the surgery-alone group; at two years it was 67% versus 50%; at three years 58% versus 44%; and at five years 47% versus 34%.

The most common major haematological toxic effects for the chemoradiotherapy plus surgery group were leukopenia (6%) and neutropenia (2%); the most common major non-haematological toxic effects were anorexia (5%) and fatigue (3%). For both treatment groups the in-hospital mortality rate was 4%, with similar post-operative complications.

"This large, randomized trial of neoadjuvant chemoradiotherapy in patients with esophageal or esophagogastric-junction cancer showed significantly better overall and disease-free survival among patients who received a chemoradiotherapy regimen based on carboplatin and paclitaxel, followed by surgery, as compared with those treated with surgery alone," write the authors. Chemoradiotherapy, they add, was associated with a

low frequency of high-grade toxic effects and could be given as an outpatient treatment.

One question that remains, note the authors, is whether oesophageal and oesophagogastric-junction tumours should be treated with preoperative chemoradiotherapy or perioperative chemotherapy.

Two trials – the MAGIC trial and the ACCORD 07 trial – found that perioperative chemotherapy provided better outcomes, the authors report. However, both included gastric tumours in addition to oesophagogastric-junction tumours.

The POET trial, which randomly assigned patients with oesophagogastric-junction tumours to preoperative chemotherapy or chemoradiotherapy might provide a better comparator, suggest the authors. Here the investigators showed a non-significant survival trend favouring preoperative chemoradiotherapy.

■ P van Hagen, M Hulshof, J van Lanschot et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *NEJM* 31 May 2012, 366:2074–84

Multidisciplinary care boosts breast cancer survival

■ **British Medical Journal**

The introduction of multidisciplinary teams (MDTs) for the treatment of breast cancer contributed to significant improvements in patient survival, a Scottish study has found.

Cancer treatment has increasingly been provided within centralised, specialist MDTs in Europe, the US and Australia, after observational evidence identified better outcomes for such organisation. It has been unclear , however, whether MDTs improve cancer survival and the clinical benefits justify the costs.

In the current retrospective study, Eileen Kesson and colleagues, from Gartnavel Royal Hospital, Glasgow, evaluated the effects of multidisciplinary care interventions for breast cancer implemented at National Health Service hospitals in the Greater Glasgow Health Board area in 1995, several years ahead of the rest of the UK.

The MDTs consisted of a specialist surgeon (performing in excess of 50 operations for invasive breast cancer each year), pathologists, oncologists, radiologists and specialist nurses. All worked to evidence-based guidelines, held weekly meetings to agree on treatments for individual patients and audited clinical activity. In other west of Scotland areas, no substantial reorganisation of breast cancer care took place until 2000, when national guidance was introduced.

Using data from the Scottish Cancer Registry, together with death records, outcomes were compared for 6050 patients who had attended hospitals offering multidisciplinary services and 7672 who attended hospitals in neighbouring areas that did not introduce multidisciplinary care until later. The comparisons were made before and after the organisational change.

Results show that before the introduction of multidisciplinary care (between January 1990 and September 1995), breast cancer mortality was 11% higher in the intervention area than the non-intervention area (HR 1.11). However, after multidisciplinary care was introduced to the intervention area (between October 1995 and December 2000), breast cancer mortality was 18% lower in the intervention area than in the non-intervention area (HR 0.82).

Subgroup analyses by age group showed the effect of the intervention on breast cancer mortality was greatest in patients aged 80 years and older (P=0.001), and significant also in patients aged 65–79 years (P=0.01). No significant effects were found for women aged less than 50 years and 50–64 years.

"Our results support the universal provision of cancer care by specialist, multidisciplinary teams," write the authors. "Further analysis of clinical audit data for multidisciplinary care could identify which aspects of care are most associated with survival benefits."

Commenting on the finding that benefits of multidisciplinary working were greatest in older patients, the authors write, "Since the intervention guidelines were not age specific, they could have given surgeons and other team members more confidence to actively treat older patients rather than managing them conservatively."

■ E Kesson, G Allardice, W George et al. Effects of multidisciplinary team working on breast cancer survival: retrospective, comparative, interventional cohort study of 13 722 women. *BMJ*, published online, 26 April 2012; doi:10.1136/bmj.e2718

Lifestyle interventions are durable in cancer survivors

■ **Journal of Clinical Oncology**

A telephone-based lifestyle intervention programme targeting diet and exercise in cancer survivors proved durable, continuing to be effective one year after discontinuation, a US study has found.

Cancer survivors are known to be at increased risk for second malignancies, cardiovascular disease, diabetes, osteoporosis and functional decline. While diet and exercise interventions have been tested in cancer survivors as a way to reduce late effects and comorbidities, few studies have assessed adherence and long-term health outcomes.

In the Reach Out to Enhance Wellness (RENEW) trial, Wendy Denmark Wahnefried and colleagues, from the University of Alabama, Birmingham, delivered a home-based diet and exercise intervention to 641 overweight or obese (BMI >40 kg/m²) survivors of breast, prostate and colorectal cancer. Participants also had to be sedentary (taking less than150 minutes of physical activity a week), over 65 years and mentally and physically able to participate. Interventions consisted of a personally tailored workbook,

telephone counselling, 15 minutes of strength training exercise every other day and 30 minutes of endurance exercise each day, daily consumption of seven servings of fruit and vegetables for women, or nine for men, restriction of saturated fat to less than 10% of energy intake and modest weight losses of less than 0.5 kg/week. A previous report by the authors showed that the intervention-group experienced significantly less decline in functional status, improvements in dietary quality, increased physical activity, and modest weight loss, compared with control participants.

The latest results show that for the immediate intervention arm there was little change in the results at the end of one year (when the intervention ceased) and the end of two years, with the exception of functional decline.

Diet quality was 66.4 at year 1 versus 65.1 at year 2, using the Healthy Eating Index 2005 criteria; weekly physical activity was 101.1 minutes at year 1 versus 100.9 at year 2; BMI was 28.2 at year 1 versus 28.2 at year 2, while physical function (according to SF-36 scores) was 74.4 at year 1 versus 70.6 at year 2.

"Data from long-term follow-up suggest that the intervention was not only reproducible but also durable. In contrast to a majority of lifestyle interventions, significant improvements in diet and exercise behaviors were observed and maintained over the 2-year study period; moreover, the modest weight loss that was promoted in this overweight sample of high-risk elders was sustained over the same period," write the authors.

In an accompanying editorial, Jennifer Ligibel from Dana-Farber Cancer Institute, and Pamela Goodwin from Mount Sinai Hospital, write, "The RENEW study adds to earlier reports by demonstrating the feasibility and durability of weight loss interventions administered at a distance to cancer survivors."

There are, however, "important caveats", they add, including the small proportion of eligible individuals who opted to participate in the study (approximately 6%), the 25% attrition rate at two years, and the fact that all study measures, including weight, were self-reported.

■ W Demark-Wahnefried, M Morey, R Sloane et al. Reach Out to Enhance Wellness home-based diet-exercise intervention promotes reproducible and sustainable long-term improvements in health behaviors, body weight, and physical functioning in older, overweight/obese cancer survivors. *JCO* 1 July 2012, 30:2354–61

■ J Ligibel and P Goodwin. NEW and RENEW: Building the case for weight loss in breast cancer [editorial]. *ibid*. pp 2294–96

Adjuvant radiotherapy helps high-risk melanoma patients

■ Lancet Oncology

Adjuvant radiotherapy improves lymph-node control in patients with metastatic melanoma at high risk of lymph-node relapse, a study from the Australia and New Zealand Melanoma Trials Group and Trans-Tasman Radiation Oncology Group (TROG) has found.

The use of adjuvant radiotherapy after lymphadenectomy to reduce the risk of further relapse has been controversial in melanoma. Early reports produced conflicting results, with the data clouded by variability in target field sizes, radiation doses and fractionation schemes. Although many major melanoma treatment centres now offer adjuvant radiotherapy to selected patients, others have remained cautious due to the absence of clear survival benefits, and concerns about the possibility of long-term radiotherapy-associated morbidity, such as lymphoedema.

In the current trial, between March 2002 and September 2007, Bryan Burmeister and colleagues, from Princess Alexandra Hospital, Woolloongabba, Brisbane, randomised 250 melanoma patients who had undergone lymphadenectomy, in a 1:1 ratio, to receive adjuvant radiotherapy of 48 Gy in 20 fractions over four weeks (n=123) or observation (n=127). The patients came from 16 hospitals in Australia, New Zealand, the Netherlands and Brazil.

Results show that, at a median follow-up of 40 months, 20 relapses occurred among 109 patients in the adjuvant radiotherapy group versus 34 among 108 patients in the observation group (HR 0.56; P=0.041). However no differences were found for relapse-free survival, where 70 events occurred in the adjuvant radiotherapy group versus 73 in the observation group (HR 0.91: P=0.56); or overall survival where 59 deaths occurred in the adjuvant radiotherapy group versus 47 in the observation group (HR 1.37; P=0.12). The most common grade 3 and 4 adverse events were seroma (occurring in nine patients in the radiotherapy group versus 11 in the observation group), radiation dermatitis (occurring in 19 patients in the radiotherapy group) and wound infections (occurring in three patients in the radiotherapy group versus seven in the observation group).

"This report confirms that adjuvant radiotherapy reduces the risk of further lymph-node field relapse after lymphadenectomy in patients at high risk of relapse, although it had no significant effect on overall survival," write the authors.

Early toxic effects related to radiotherapy, they add, were infrequent and minor. "If the intention of treatment is to reduce the risk of regional recurrence, adjuvant radiotherapy is a treatment option that should be discussed with patients at high risk of lymph-node field relapse after lymphadenectomy."

Future studies, write the authors, should centre on exploring the role of radiotherapy in the preoperative setting, where modern imaging modalities could be used to identify high-risk patients before surgery.

In an accompanying commentary, Roger Macklis, from Cleveland Clinic, Ohio, writes that it will be important to explore the addition of targeted melanoma agents such as ipilimumab and vemurafenib to local-field radiotherapy. One hypothesis, he adds, suggests that radiation effects result in heightened presentation or processing of immune system targets.

■ B Burmeister, M Henderson, J Ainslie et al. Adjuvant radiotherapy versus observation alone for patients at risk of lymph-node field relapse after therapeutic lymphadenectomy for melanoma: a randomised trial. *Lancet Oncol* June 2012, 13:589–597

■ R Macklis. Finally, a substantial role for radiotherapy in melanoma. *ibid*, pp 561–562

Low-dose radioiodine is effective against thyroid cancer

■ New England Journal of Medicine

Two separate studies published in the same issue found that low-dose radioiodine protocols used in patients with low-risk thyroid cancer had similar rates of successful tissue ablation as conventional protocols. Taken together, the results of the French and UK investigations suggest radiation doses could now be cut, write the authors of an accompanying editorial.

Radioiodine is administered to patients with thyroid cancer after total thyroidectomy for three reasons. First to eradicate normal-thyroid remnants in order to achieve undetectable serum thyroglobulin levels, second to irradiate any neoplastic focus in order to decrease the risk of recurrence; and third to perform total-body scanning for persistent carcinoma. Adverse effects of using high doses of radioiodine include patients staying in hospital isolation units for at least two days, lacrimal and salivary-gland disturbances and an increased risk of developing secondary cancers.

In the first study, funded by the French National Cancer Institute and the French Ministry of Health, Martin Schlumberger and colleagues, from the Institut Gustave Roussy, Villejuif, randomly assigned 752 patients with low-risk differentiated thyroid carcinoma to undergo one of four strategies, each combining one of two methods of thyrotropin stimulation – administration of recombinant human thyrotropin or thyroid-hormone withdrawal – and one of two 131I activities (1.1 GBq or 3.7 GBq). Patients were recruited from 24 centres between 2007 and 2010, with thyroid ablation assessed eight months after radioiodine administration by neck ultrasonography and measurement of recombinant human thyrotropin-stimulated thyroglobulin.

Results show that, of the 684 patients with data that could be evaluated, thyroid ablation was complete in 631 (92%). The thyroid ablation rates were found to be similar between the four groups – 90% for patients treated with recombinant human thyrotropin who received 1.4 GBq, 93% for patients treated with thyrotropin who received 3.7 GBq, 92% for patients treated with thyroid hormone withdrawal who received 1.4 GBq and 94% for those treated with hormone withdrawal who received 3.7 GBq.

"Thus, the use of recombinant human thyrotropin and a low dose of 131I for postoperative radioiodine ablation represents an effective and attractive option for the management of low-risk thyroid cancer that reduces the amount of whole-body irradiation and maintains the quality of life," write the authors.

In the second study, done by Cancer Research UK, Ujjal Mallick and colleagues, from Freeman Hospital, Newcastle upon Tyne, compared low- and high-dose radioiodine (1.1 GBq and 3.7 GBq, respectively) in combination with thyrotropin alpha or thyroid hormone withdrawal before ablation. The study was undertaken in 438 patients with T1 to T3 thyroid tumours with possible spread to nearby lymph nodes, but no metastasis.

On analysing the data for 421 patients, researchers found that low-dose radioiodine was as effective as high-dose radioiodine (ablation success rates of 85.0% vs 88.9%). Comparing the groups treated with thyrotropin alpha with those treated with thyroid hormone withdrawal, ablation success rates were also similar (87.1% vs 86.7%).

Breaking the results down further, low-dose radioiodine plus thyrotropin alpha showed a success rate of 84.3%), compared with 87.6% for high-dose radioiodine plus thyroid hormone withdrawal and 90.2% for high-dose radioiodine plus thyrotropin alpha.

But significantly more patients randomised to high-dose radioiodine had hospital stays of three days or longer (36.3% vs 13.0%, $P<0.001$). The higher dose of 131I was associated with a higher rate of adverse events (33% vs 21%, $P=0.007$). Adverse event rates did not differ by method of thyrotropin stimulation.

"Our study answers two central questions involving radioiodine ablation of thyroid remnants after surgery for differentiated thyroid cancer: namely, that the efficacy of low-dose radioiodine is similar to that of high-dose radioiodine, and that the efficacy of low-dose radioiodine ablation is not compromised by the use of thyrotropin alfa instead of thyroid hormone withdrawal," write the authors.

In an accompanying editorial Erik K Alexander and P Reed Larsen, from Harvard Medical School, Boston, write, "These results should change standard practice, although they also raise the question of whether any radioiodine therapy is required for low-risk patients, since 21 to 59% of the patients in these two studies had already met the goal of a low thyroglobulin level after thyroidectomy alone."

The future hope, they add, is that identification of a pattern of gene expression or patient characteristics associated with a higher risk of recurrence might allow more-aggressive treatments to be focused appropriately.

■ M Schlumberger, B Catargi, I Borget et al. Strategies of radioiodine ablation in patients with low-risk thyroid cancer. *NEJM* 3 May 2012, 366:1663–73

■ U Mallick, C Harmer C Yap et al. Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. *ibid* pp 1674–85

■ E Alexander, P Reed Larsen. Radioiodine for thyroid cancer – is less more? *ibid*, pp 1732–33

myworld

Ruth Conroy is a specialist registrar in clinical oncology at the Christie Hospital in Manchester, UK. She came first out of a class of 62 young oncologists from 28 countries in the learning assessment test at the end of this year's ESO Masterclass in Clinical Oncology.

Why I chose to work in oncology...

I didn't have much exposure to oncology as a medical student or a junior doctor so I think it held an air of mystery that made me want to find out more. I really enjoyed my first oncology job and I've been hooked ever since.

What I love most about my job...

I love the variety and the patient contact. It means no two work days are ever the same.

The hardest thing about my job...

Patients' expectations are growing and with new drugs being developed all the time it is getting increasingly difficult to talk about what comes next when treatment options are exhausted.

What I've learnt about myself...

I'm not very good at switching off from work but with such a demanding job it is very important to do so and I've realised how important it is to maintain activities outside work.

I'll never forget...

The sight and smell of my first fungating tumour! Whilst I was planning the radiotherapy with my consultant I did not have much faith that we were going to be able to do much to help, but on seeing the patient again in a few months it really brought home to me what a massive impact we have on people's lives.

A high point in my career...

Obviously coming first in the Masterclass exam was a high point! Also my first oral presentation at a conference, as it made me realise how much I'd progressed in my career and that all the hard work pays off in the end.

I wish I were better at...

Many things! Music would be up near the top of the list, I've always admired those who can just pick up a guitar and play a tune. Hopefully one day I'll find the time for lessons.

The most significant innovation in my specialty in recent years...

It is difficult to pick just one but I think throughout my career I have seen vast changes in imaging techniques. As a medical student even CT was a somewhat precious commodity and it wasn't until I started work that I came across PET- CT, which is now part of the routine work-up for many cancer sites. As a clinical oncologist it is exciting to hear of new techniques that might help with target delineation for radiotherapy planning to reduce toxicity.

What I value most in a colleague...

Honesty and reliability. I've found most problems can be sorted as long as people are honest about the situation. I don't expect my colleagues to have all the answers, but I want to know that I can rely on them to do their fair share of the work.

My advice to someone entering my specialty today would be...

Enjoy it. Starting a new job can always seem overwhelming but you are not expected to know everything on your first day so enjoy spending time with your patients at difficult times in their lives, and also being able to be at the cutting edge of medicine.

What I wish I had learnt at medical school...

That it is OK to not know the answer and that sometimes there is no right answer! Patients and their illnesses have not read the textbooks so may not follow the rules, so it is important to involve the individual when planning their treatment.