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European School of Oncology
Learning to care

cancerworld

LIVING IN THE PRESENT

How mindfulness is helping patients live life in the face of sadness, stress and fear

BIOLOGY IN THE BUNKER

We lift the lid on the hidden world of translational radiotherapy

AGE DISCRIMINATION

Is 'staving off the evil hour of death' a right at any age and at any price?

Christopher Wild

Let's be practical

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Cancerworld

Shaping the future of cancer care

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Action for access

KATHY REDMOND EDITOR

The EU Patient Access Partnership was launched at the beginning of October in response to growing inequities in access to medical treatments that are resulting from cuts in public spending, particularly in countries of southern and eastern Europe. Building on the 2013 Vilnius Declaration on Sustainable Health Systems in Europe, this partnership aims to ensure that European citizens gain access to high-quality and safe healthcare, regardless of where they live. This includes access to modern and cost-effective medicines.

The European Society for Medical Oncology (ESMO) has taken up this call with the development of a rating scale to evaluate the magnitude of benefit of new anti-cancer drugs. Based on a similar concept to WHO's Model List of Essential Medicines for low- and middle-income countries, its purpose is to improve access to important new therapies by helping decision makers differentiate those that offer major benefit to patients from those with only incremental value.

Factors taken into consideration in this rating scale include overall survival, progression-free survival, hazard ratio, long-term survival, response rate, prognosis of the condition, quality of life and toxicity. Cost has not been taken into account because of the heterogeneity of health systems across Europe.

While this initiative is to be welcomed, other efforts are required to make our health systems more sustainable. The pharmaceutical industry needs to develop innovative pricing models that take account of the differences in ability to pay between EU Member States, and policy makers need to ensure that companies are not penalised unduly by introducing differential pricing.

All of us in the European cancer community need to play our part, and we have much to learn from the US-based Choosing Wisely Campaign, which the American Society of Clinical Oncology (ASCO) has signed up to.

Defining value in cancer care is a key component of this initiative. ASCO is recommending five things physicians and patients should question, including the choice of anti-emetic drugs, combination chemotherapy in advanced breast cancer, the use of PET or PET-CT as part of routine follow-up care in asymptomatic patients, the use of PSA testing in men with no symptoms of the disease, and the use of therapies targeted against a specific genetic aberration in patients whose tumour cells do not express a specific biomarker that is predictive of response.

The mantra is that wisdom should prevail in clinical decision making, and making best use of limited resources does not necessarily translate into worse patient outcomes. If we all play our part in cutting spending where it is least effective, we can help ensure the sustainability of our healthcare systems and address the current unacceptable inequities in access to high-quality cancer care that persist in Europe. ■

Christopher Wild: Let's be practical

SIMON CROMPTON

Understanding how cancer wreaks its havoc on the human body is important for the head of the International Agency for Research on Cancer, but his main concern is how to stop it.

In the 30 years he has worked in research, Christopher Wild has been asked many times whether there will ever be a cure for cancer. It is astounding, says the Director of the International Agency for Research on Cancer (IARC), that no one has asked him whether cancer will ever be prevented.

"We are not going to treat our way out of cancer," he tells me, echoing the words he used in February, when IARC published a World Cancer Report revealing that the worldwide cancer burden is expected to rise from 14 million new cases a year in 2012 to a staggering 22 million a year by 2030.

Around 50% of the world's cancer cases are preventable based on current knowledge, says IARC. And Wild tells me he estimates that around 90% of cancers have an environmental or lifestyle cause – it's just that we don't understand the detail yet. So getting to grips with causes and effects transforms the prospects of winning the global cancer battle.

It's not surprising, then, that Wild feels perplexed that research and funding are currently so concentrated on treatment, not prevention. "Maybe it's because most people come across cancer when they or someone they know has got the disease, and the first question they ask is 'Can it be cured?'

"The people who donate to cancer charities mainly do it on the basis that they want to see cures, and that resonates through the charities. It drives their research investment. Governments, universities and the private sector see the economic opportunities in developing new treatments, whereas there is much less money to be made from prevention. These factors combine so that in many Western countries the proportion of cancer research money spent on understanding causes and prevention is a small fraction. And once the direction of travel is started, it continues to be reinforced."

Wild, now in his second five-year term as director of IARC, is nothing if not ambitious for his remaining four years. He wants to re-orientate the global cancer research agenda towards prevention.

And as we sit in the IARC offices in Lyon, France, talking about the prevention priorities – researching how best to implement current knowledge, resourcing measures that are known to work, introducing regulation and legislation – all those astonishing predictions about the global rise of cancer seem less of a cause for despair. Once you look at cancer with a global perspective, there is a world of high-impact measures to be taken without waiting for miracle treatments.

"The number of cases that could be prevented, particularly in low- and middle-income countries, is huge compared with the incremental effect of improved treatment," he says. "At the same time, we're clearly not going to discover the cause and be able to prevent every cancer, so the second arm of our approach is early detection to make the treatments we have more effective."

Wild, a pharmacologist who evolved into a molecular epidemiologist, observes he is motivated by problem-solving rather than the straightforward curiosity that drives many scientists. Since his first association with IARC as a postdoctoral fellow in 1984, his interest in the interplay of environmental, lifestyle and genetic risk factors in causing cancer has evolved, and his fit with the agency has become ever closer.

IARC, part of the United Nations, is the specialised cancer agency of the World Health Organization. It fosters collaboration in cancer research across countries and organisations, bringing together skills in epidemiology, laboratory sciences and biostatistics to identify the causes of cancer so that preventive measures can be introduced.

It has a particular interest in developing collaborative research projects in low- and middle-income countries, where the rise in cancer is fueled particularly by infections, tobacco, alcohol, air pollution and poor diet, among other factors. Around seven of every ten cancer deaths occur in Africa, Asia, and Central and South America.

A Francophile Englishman, Wild has been at

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"Clear findings can lead to practical interventions, such as clean burners replacing indoor fires"

IARC's Lyon headquarters for 17 years of his career, and proudly recounts the agency's idealistic origins shortly after the Second World War. Emmanuel d'Astier de La Vigerie, a former French Resistance leader who founded the *Liberation* newspaper and became a politician, was haunted by a letter written by a man who had just lost his wife to cancer, who asked him: "You may be fighting for political causes and peace, but what about fighting this terrible disease?"

D'Astier de La Vigerie called on General Charles de Gaulle, the French President, to act, and the result was a proposal that the major world powers – Australia, France, Germany, Italy, the Soviet Union, the United States, the UK – should levy half a per cent of their military budgets to "found an international institution dedicated to the combat for life, under the effective control of qualified UN institutions". IARC came into being in May 1965 and was installed in Lyon in 1967 – close to the World Health Organization in Geneva.

Wild laughs at the prospect of IARC still receiving that amount of money from defence budgets: "Can you imagine what we could do!" Today IARC is funded by any WHO member state that chooses to participate – 70% of IARC's budget is divided equally between participants, with 30% divided according to each country's contribution to the WHO budget, roughly corresponding to their economic status. The budget for the next two years is more than €40 million, and there are 24 participating states.

It is still an act of generosity for these countries to look beyond national self-interest and donate to a global good, says Wild. But it makes sense that the countries who are members can contribute to the mission of IARC through their scientific expertise, joining with IARC scientists to study cancer anywhere in the world. Recently IARC has increased the involvement of developing countries in its decision-making, through dialogue with countries not represented on its governing body.

"I think that everyone is enthusiastic about emerging economies participating in collaborative efforts, and as a result, their research base is developing. So it's an exciting time for us."

Wild believes that IARC's role in leading the global research agenda can only grow: its positioning alongside WHO and its track record of working worldwide means it is trusted, independent and immaculately connected. But while its research focus and small governance structure mean it is relatively free of the lumbering politics of world health, Wild is also aware that if IARC's important findings are to be acted upon, they have to be presented to national and global bodies in a relevant and accessible way.

He knows, for example, that IARC's monographs evaluating carcinogenic risk to humans are already well used by governments for protecting populations. Since the early 1970s, IARC has convened working groups of experts to evaluate evidence on chemicals, biological factors and lifestyle influences believed to be linked to cancer. This has resulted in 111 advisory monographs, direct in style and with clear conclusions.

One of the latest concludes that outdoor air pollution from transport, power generation, industry, domestic heating and cooking is "not only a major risk to health in general, but also a leading environmental cause of cancer deaths" – from bladder as well as lung cancer. Around 1 in 10 lung cancers may be associated with air pollution (including smoke inhaled from indoor fires in developing countries), it found. Such clear findings can lead to practical interventions such as clean burners replacing indoor fires, the reduced use of diesel generators and more stringent regulations on industry and transport.

In recent years, IARC has been working more closely with WHO and other partners to ensure that the research it produces will be used. IARC produces handbooks of cancer prevention, evaluating the scientific evidence on the protective effects of interventions such as sun protection or weight control. As part of this programme,

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an IARC working group is about to examine the benefits and risks of breast cancer screening, and Wild has been discussing with WHO how to ensure that the scope is correct, and that the outcomes are clearly presented and easily incorporated into policy guidelines.

This appreciation of the need to bring science down to a human level isn't simply a pragmatic understanding of good communication on Wild's part. For him, seeing the people at the receiving end of science has had a profound effect on his motivation and career direction.

When he completed his pharmacology degree at Manchester University in 1980, Wild felt at a loss what to do next. He hadn't particularly enjoyed the course and hadn't a clue how to use his new qualification. So he took the advice of a scientific supervisor and began a PhD based at the Christie Cancer Hospital in Manchester, making monoclonal antibodies to study damaged bases of DNA in cultured cells.

It wasn't this lab work which determined his career, however – it was the walk he took to the cafeteria every lunchtime.

"I had to pass by the children's ward," he says. "And the emotional reaction I had to those young people made me realise that what I wanted to do on a very simple level was help people with this disease. I knew I was not a mechanistic person excited by how things work fundamentally. I needed to see a problem and bring the necessary tools to bear."

He completed his thesis, failing to see the relevance of his lab work and believing that science was not for him. But a PhD supervisor who had completed a post-doctoral fellowship with IARC suggested that Wild did the same. "I thought a year in Lyon sounded quite nice," he says. "I'd always liked France and the language."

About the same time he realised that the antibodies he had been working on could be used as sensitive tools for determining exposure to carcinogens in the environment, particularly nitrosamines, which were suspected to cause oesophageal cancer. His application went in, and then everything fell into place.

"First, I discovered the relevance of my subject – I found it incredible that you could measure changes in people who had been exposed to toxins and then do something to counter it. And then I met the people from all over the world at IARC who were not thinking about career development but were there because they wanted to solve the problem of cancer. Their way of working was an inspiration."

It wasn't long before Wild discovered the importance of epidemiology – his supervisor correctly informed him that the identification of most human carcinogens was due to epidemiological studies. So at IARC he began carrying out field work with epidemiologists, applying his laboratory methods to biological samples.

His first trip to Africa was hugely formative, again because it brought the human factor into science. A clinician colleague took him to meet liver cancer patients in a hospital in The Gambia, West Africa – people affected by carcinogens such as dietary toxins and hepatitis viruses.

"The first person I met has really stuck with me. He was an old man, dying, who had a hugely distended abdomen. And I was standing there, a white man in a white coat in the clinic, and the look he gave me said: 'This is the man who is going to solve my problem.' He was desperate. And I felt absolutely useless, a spare part. I wasn't a medical doctor and there weren't even adequate painkillers available for him. Later

Infection rates among children are now 20-fold lower than before the vaccination programme

I realised he was in his early 30s."

It provided more motivation. The question to answer was: "Can you develop tests to measure exposure to carcinogens, and then use that information to reduce exposure?" He concentrated on exposure to naturally occurring aflatoxins (a type of mycotoxin), commonly found in poorly stored peanuts and a known cause of liver cancer, which accounts for 25% of male cancer deaths in west Africa and frequently kills people before they are 45. He developed a blood test that measured aflatoxin exposure which, he says, has "transformed our ability to link exposure to disease outcomes".

"So that's been the crux of my career – taking the latest advances in laboratory science and, rather than leaving them to take their natural route to the clinic, trying to drag them out into population-based work to understand the causes of a condition, and then use similar biomarker methodologies to evaluate interventions." In Africa, for example, Wild and his colleagues demonstrated through blood tests that in the villages where farmers had been provided with expertise in storing and processing their peanut crop, exposure to aflatoxins was reduced by 60%. It's been gratifying seeing results, says Wild.

Another striking outcome came from IARC's work in The Gambia in the mid-1980s. Alongside mycotoxins, the other major cause of liver cancer in Africa is hepatitis B. IARC began an infant vaccination trial – knowing that it would have to wait at least 40 years to gauge its impact on cancer rates in adults. But already, 30 years on, research has found that hepatitis B infection rates are now less than 1.0% among young Gambian children compared with 15% in the '80s – that means infection rates among children are now 20-fold lower than before the vaccination programme.

Wild rose up the IARC ranks, becoming head of its Unit of Environmental Carcinogenesis when he was just 34. His only career foray out of Lyon, other than a year's fellowship at the Netherlands Cancer Institute in the mid-1980s, came two years later, when he was offered the opportunity to become the first Chair of Molecular Epidemiology at the University of Leeds, in the UK. He stayed there between 1996 and 2008 – setting up the Leeds Institute of Genetics, Health and Therapeutics, and seeing his three children through their schooling. The academic setting was "another world" he says, but when the IARC director's job came up, he took stock. "I suddenly realised my computer wallpaper was Lyon. The pictures on my wall were Lyon." It was clear where he wanted to be, and his wife, a neuroscientist, gave up a job in NHS clinical trials to come and share the new challenge with him.

Today, he highlights two priorities for IARC. The first is to improve cancer registries. "People don't get very excited about cancer statistics, but it's the foundation of cancer control. If you don't know the patterns of cancer in a particular country, or the projections, how do you know where to invest your money? We've been trying to improve the quality of cancer registration for 40–50 years." Less than 10% of the African population is covered by cancer registries.

For the past four years IARC has been implementing a new model to encourage registration, setting up regional hubs responsible for developing registries and providing training and resources. There are currently four hubs, with more to come. A hub in Mumbai, for example, is supporting the development of cancer registries in Central, Eastern and Southern Asia. Wild believes there are already signs of "significant movement" to improve the quality of data informing policy.

The second challenge is to address the gaping holes in current cancer knowledge, particularly in the area of implementing prevention strategies. It is frustrating, says Wild, that although some cancer prevention strategies – such as screening or vaccines – are known to be effective, getting them operational in low- and middle-income countries, where resources are limited, is often incredibly difficult. For example, even

though IARC classified mycotoxins as dangerous human carcinogens two decades ago, and despite evidence that they contaminate much of the diet in the developing world, national governments have done very little to confront the problem.

"There are barriers to implementation we don't understand, and to me that's a very neglected area of cancer research," says Wild.

IARC is aiming to conduct more formalised studies into how to convert good ideas into good practice. It has been working with the Thai government, for example, to examine participation in its colorectal cancer screening programme. Its research revealed that there was higher participation in rural than urban areas, and that women were more likely to take part than men, and this information is being used by the government to refine the programme as it up-scales nationally.

Another important initiative has been in HPV (the human papilloma virus). HPV causes cervical cancer, the fourth most common women's cancer globally. In sub-Saharan Africa, the annual cervical cancer death rate is 22.5 per 100,000 women compared with 2.5 per 100,000 in North America. The current vaccination schedule is three spaced doses – but this presents implementation problems, particularly cost and compliance. IARC has been studying whether two doses provide a similar response to three. The indications are that they do, so WHO is now recommending a two-dose regimen. "That will have a huge impact on access to the vaccine in high cervical cancer regions."

There are a hundred and one potential prevention measures on hold because of lack of research. It is striking, says Wild, that when IARC experts come together to review evidence for monographs or handbooks on prevention, it rapidly becomes clear that studies cluster in particular areas, and some research is repeated over and over again. "There are glaring gaps, and IARC tries to point out the research priorities. But if someone took a global overview, and coordinated plugging the gaps, we'd all be much more efficient."

Wild knows there are priorities beyond prevention: in many developing countries there is no access to basic medicines or palliative care, so even small treatment improvements can go a long way. Improving early detection therefore has to be a priority with common cancers where cause is poorly understood, such as prostate cancer, or where primary prevention measures are difficult, as with breast cancer (where rising rates are due in part to women having fewer children at a later age and breast feeding less).

"Maybe it's my optimistic nature, but I don't think it's a hopeless situation. I think there is lots we can do in the face of these projected rises." Incidence of breast cancer has been soaring in low- to middle-income countries, with the annual rate of new cases predicted to rise by a further 60% over the next 20 years. A clear strategy for the early diagnosis and treatment of breast cancer in these countries would make a huge difference, Wild believes.

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The IARC biobank contains biological samples from research studies conducted all over the world

"In countries like South Korea, which had no national screening programme for breast cancer, we saw huge improvements in survival because the cancers are being caught earlier through awareness and patients getting access to the right treatments quickly."

Wild's optimism springs to life when he points out that the very fact that cancer rates vary so much internationally testifies to the possibility of reversal. In much of eastern and southern Africa, oesophageal cancer is the most common cancer in men, yet there is hardly a case in West Africa. Similarly, colorectal cancer has been historically common in the United States population of East Asian origin, yet rare in Japan.

"We need some high-level thinking about areas of research that must be independent of industry, and how to fund them"

"So if you take all those countries where a given cancer is at its lowest rate, that is presumably the rate that isn't due to the environment or lifestyle. The rate above that must be modifiable. That's where the hope comes from."

Even if IARC managed to put its finger on all the modifiable cancer factors, however, Wild believes some actions simply have to be enforced to control cancer. No longer does he

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believe that people simply change their behaviour if you point out to them that what they are doing is dangerous. The pressures on people to consume are so great that policy and regulation are the most effective means of change, he believes. Increasing the price of cigarettes is the most effective smoking control measure, and if all countries implemented the WHO framework convention on tobacco control "there would be a big impact".

Similar measures would help cut alcohol consumption, and regulation is part of the answer to air pollution, says Wild. And though he is reluctant to be drawn too far on regulating the food industry, he feels nutrition is the next "big challenge".

"There's debate at the moment around taxation on sugary drinks and energy-dense foods. Sometimes policy runs ahead of the evidence, so again we need to design studies and measure the impact of these sorts of interventions."

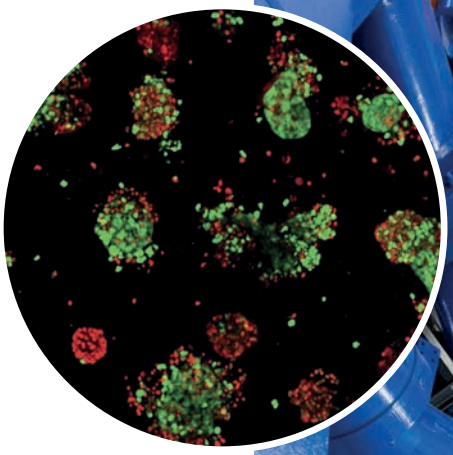
But he acknowledges that industry has not always helped answer such questions, and has sometimes complicated them. "I'm aware that if you don't have industry funding for nutrition research, it's very difficult to conduct studies at all and there's great emphasis on academic collaboration with industry in some countries. At the same time, governments want independent advice. So I think there has to be some high-level thinking about areas of research that need to be independent of industry and how to fund them." He mentions IARC's research into HPV vaccination as an example of research that has been influential because of its independence from industry.

Towards the end of the time allocated for our interview we talk more informally, comparing notes on our similar upbringings in Manchester and our playground experiences pretending to be Manchester United players – Wild still played football until he turned 50, and even now he says watching it "keeps me going". He tells me about the strong Christian faith he developed at university, and how he continues to be intrigued by how you put Christian principles into practice in a scientific setting.

And he tells me how he has tried to nurture a set of values that IARC uses in all its interactions with organisations and people: courtesy, honesty and generosity. "It's not just what we do, but how we do it that's important – because as an international agency people are putting trust in you." It's another example of Wild's personal determination not to let cool science or hard politics lose sight of the people it is designed to help, or the people who make it happen.

"I want to leave the agency with a good infrastructure, a mission and an adapted scientific programme that will equip it for at least the next 20 years. Then I will walk away very satisfied, I think." ■

Biology in the bunker



MARC BEISHON

Advances in imaging and molecular biology are opening up a wealth of new avenues for research and treatment in radiotherapy. But could progress be held back by a lack of public awareness of the potential for innovation?

About half of people diagnosed with cancer in developed countries are likely to receive radiotherapy as part of their treatment, so improving the safety and efficacy of radiotherapy is central to the overall cancer research effort.

But advances in radiation oncology are largely hidden from public view, which is not helping the field to obtain funding. A survey of people in Britain, for example, found that only 10% thought radiotherapy was a "modern, cutting edge treatment" as opposed to 40% for cancer drugs. Only occasionally, such as with a perceived shortage of proton machines, does the latest technology make news; more likely, there will be publicity for a lack of standard radiotherapy care.

In reality radiotherapy has contributed a great deal to progress against cancer over recent decades, not least through major advances in the technology of conventional radiation delivery, with the arrival of systems such as IMRT and IGRT (intensity modulated and image guided radiotherapy), and also arc therapy, that allow higher doses on more precise volumes and spare more normal tissue. New treatment approaches that combine radiation with chemotherapy have now become a standard of care in a number of cancers. And with more advances in molecular biology opening up new avenues to explore, radiation oncology seems particularly lively at present, despite a lack of funding.

Record numbers of abstracts on clini-

At this ion-beam facility in Heidelberg, researchers are exploring ways to better tailor radiotherapy to each tumour's biology as well as anatomy

HEIDELBERG ION-BEAM THERAPY CENTRE (HIT)

cal trials and studies – nearly 2,900 – were presented this September at the conference of the American Society for Radiation Oncology (ASTRO). Europe's own radiation oncology society, ESTRO, also had a successful conference this year, with more than 5,000 participants, and the radiation oncology group in the EORTC – Europe's largest collaborative cancer clinical trials organisation – has a number of important collaborative trials running or about to start.

There is broad agreement among radiation oncologists about current clinical standards and areas of research that are ongoing and that show most promise. As with drug development, the aim is to provide more precise and personalised treatment, given radiotherapy's long history as a 'one size fits all' approach and as essentially a single physical technology which can kill cancer cells but which can also severely damage normal tissue.

The main research work can be seen in two categories, biology and physics, with extensive overlap between the two.

Precision targeting, photons to ions

Improving the precision of radiotherapy is certainly one of the major branches of medical physics. Amir Abdollahi, head of the Max Eder translational radiation oncology research group at Heidelberg, Germany, points to IMRT as "among the first big steps in precision for targeting tumours".

"Conformal irradiation of tumours, using up to nine or more irradiation angles, allows for higher doses while sparing critical organs at risk, close to the tumour margin. However, this benefit is bought at a higher volume of normal tissue receiving a lower dose of irradiation," says Abdollahi. This technique is proving to be especially useful in improving the quality of life in patients with cancers such as head and neck, he says, and with rapid progress in radiotherapy software and hardware cutting the cost and time needed for IMRT, it is increasingly used in many cancer types.

IMRT is essentially a technological advance, as is the use of particles in the form of protons, which Abdollahi describes as "the next step" in applying more precise doses to tumours. Proton therapy is not very different from photon radiation in terms of DNA damage complexity and tumour cell kill, he says. "However normal organs at risk can be much better spared compared to conventional photon irradiation, and also the volume of normal tissue receiving a lower radiation dose can be significantly decreased."

The latter is of great importance for paediatric oncology, he adds, where secondary cancers could be of concern.

"Now we are working with larger particles at Heidelberg. In addition to the precision of protons, heavier ions such as carbon ions can densely ionise surrounding tissue, generating irreparable DNA damage. Their efficacy may also be less dependent on tumour oxygenation levels, making it easier to eradicate radioresistant hypoxic tumour cells," says Abdollahi. Other potential radiobiological differences need to be systematically investigated in comparison with proton and conventional radiation, he says.

A wealth of biological ideas

There is a wide spectrum of translational research underway using the different forms of radiation techniques and qualities, and also advanced imaging techniques.

The biological work falls into several camps, says Abdollahi, and includes overcoming hypoxia in tumours; radiosensitisers that enhance the effect of radiation; chemotherapy and targeted drugs that can cooperate with radiation;

"Drug companies are often reluctant to fund trials that use their products in chemoradiation combinations"

gene signatures that could predict sensitivity to radiation; agents that offer protection for normal tissue; and novel areas such as angiogenesis and immunotherapy in tumour–stroma communications, where researchers are also looking to 'modulate' radiation in various ways.

The complexity of research varies. There are studies of radiation with existing targeted agents, such as inhibitors of the EGFR pathway, to see whether it is still beneficial in combination with particle therapy. "This is a straightforward translational question," says Abdollahi. More complex is finding causal links, or pathways, that are affected by radiation and using those pathways to sensitise cells to radiation.

Hypoxia

Take hypoxia, which is a long-standing area of study and which has been an obvious phenomenon to attack because it is a common reason for the failure of local treatment. Conventional radiotherapy works by damaging the DNA of dividing tumour cells, mostly through the action of free radicals that are promoted by oxygen. But as solid tumours often restrict oxygen through a poor blood supply, they also develop radioresistant areas that can be unstable and change in location and time.

Hypoxia can render tumour cells two to three times less susceptible to radiation. A number of approaches over almost 50 years have been tried to overcome it, including hyperbaric oxygen, sensitising drugs such as nimorazole, and hypoxia-activated cytotoxic drugs that target hypoxic cells.

Despite this effort and scores of trials, Jens Overgaard, a European expert in the field at Aarhus University Hospital, Denmark, lamented in 2007 that hypoxic radio-sensitisation is "adored and ignored". Although "ample data exist to support a high level of evidence for the benefit of hypoxic modification... [it] still has no impact on general clinical practice," he wrote in the *Journal of Clinical Oncology* (vol 25, pp 4066–74).

Work of course continues, especially in head and neck cancers, as hypoxia is such an important response predictor. Investigators are using techniques such as PET imaging with tracers to identify hypoxic areas and then target them with radiation 'dose painting' (see opposite). This could help stratify patients into higher risk groups for precise, higher doses. Other researchers are looking at genomic signatures of hypoxia that could identify people most likely to benefit from the radiosensitiser, nimorazole.

As Jacques Bernier, director of radiooncology at the Genolier Clinic in Switzerland, points out, hypoxia is a key area for the crossover between physics, biology and also computer science: "Radiation dose painting to target intratumoural radio-resistance levels is likely to be more and more used thanks to the increasing sophistication of radiation planning and delivery tools," he says.

Chemoradiation

Radiosensitising drugs are a major research field on their own, as are chemotherapy and targeted anti-cancer agents that can have a synergistic effect with radiotherapy, including acting as radiosensitisers.

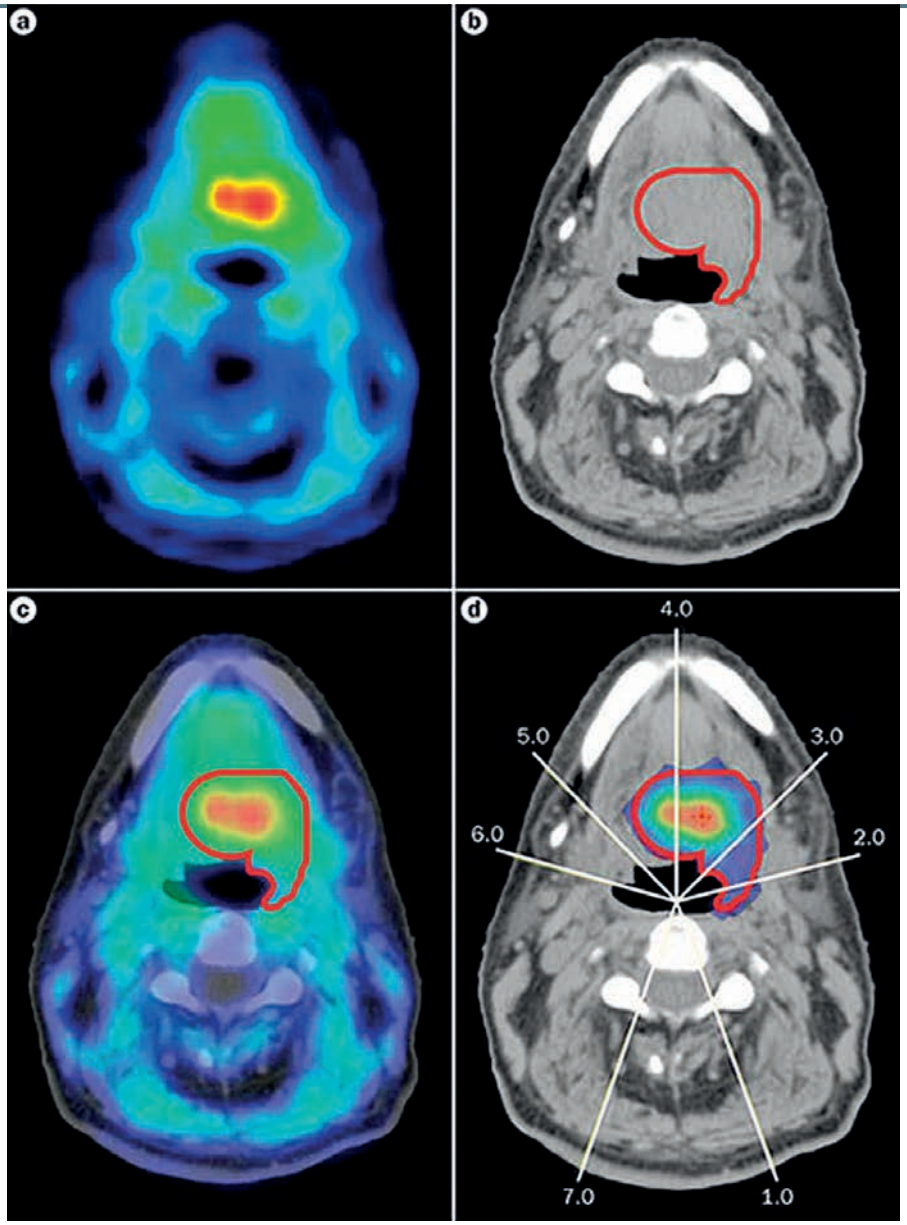
There has been considerable success with chemoradiation, as Bernier notes. "Concomitant chemoradiotherapy is now applied in large populations of patients presenting with locally advanced disease in brain, head-and-neck, lung, uterus and various digestive tract malignancies," he says.

Drug–radiation interactions have now been studied for several decades "in terms of spatial cooperation, cytotoxic enhancement, biological cooperation and temporal modulation," he notes. An outstanding example for a newer targeted agent – likely to be mentioned by any oncologist – is the combination of radiotherapy with an anti-EFGR drug in head and neck cancers, as EGFR is almost always overexpressed in squamous cell carcinomas in these sites.

"It's a wonderful example of successful translational research – in a significant number of patients with head and neck carcinoma, the use of bioradiation with cetuximab is nowadays acknowledged as level I evidence by bodies such as ESMO," says Bernier. (For a paper on milestones in chemoradiation see *JCO* 2014, 32:1173–79, which also describes how cisplatin became a standard in head and neck cancer.)

Obstacles and slow progress

Despite its clear potential, it is proving hard to find funding to back research into chemoradiation. Abdollahi says there is little support from the major makers of radiotherapy equipment, while drug companies are often reluctant to fund trials that use their products in chemoradiation combinations, as they see little prospect of ben-



Combining FAZA-PET tracer imaging which reveals areas of hypoxic (radioresistant) cells (a), with CT imaging to delineate the tumour anatomy (b), makes it possible to plan the dose for each of seven intensity-modulated radiation fields to give the most biologically effective dose distribution (d)

Source: MR Horsman et al. (2012) *Nat Rev Clin Oncol* 9:674-687, by permission from Macmillan

efit. This is particularly true where older off-patent agents are used, but even with newer agents, the quantities involved tend to be far smaller than when the same agent is used as a standalone medical therapy.

The fact that many agents of interest have only been investigated in patients with advanced cancer presents an added hurdle, says Abdollahi. "Radiotherapy has one of the most attractive populations for investigating combination regimens. In addition to improving local tumour response to irradiation, patients with locally advanced cancer and a poor prognosis (e.g. with lung or pancreatic cancer) may benefit from concurrent and maintenance pharmacological treatments by preventing the formation of distant tumour metastases." Yet most new compounds are investigated in heavily pretreated end-stage patients who have already developed disseminated metastases, he says, as these populations are larger and therefore of more interest to pharmaceutical companies.

Investigators therefore have to go back to square one and conduct toxicology studies on combinations, as a drug that is of low toxicity on its own may be more toxic when used with radiation. And this is leading to bottlenecks at the preclinical to phase I stages, says Abdollahi. It is ironic, he notes, that new classes of drugs, DNA-repair inhibitors such as PARP, are investigated in phase III trials in combination with chemotherapy rather than radiation, despite the fact that they work in a complementary way.

Commenting though on what we can expect in the future, Bernier says: "It is too early to say what will be the exact place of combination of radiation with targeted therapies, despite the success of anti-EGFR-based bioradiation."

Philippe Lambin, medical director at the Maastro Clinic, a radiotherapy institute in the Netherlands, adds that another major barrier to the research is effects on normal tissue. "We need preclinical studies on both tumours and normal tissue, as you must get

"Radiotherapy has one of the most attractive populations for investigating combination regimens"

"Genomic signatures can show who may avoid or receive less radiation"

the therapeutic ratio right – in practice you always irradiate normal tissue – but there are few labs in the world that can do this," he says. "We should have certified labs where we can do these experiments." Current chemoradiation regimens are often at the limits of toxicity, although additive toxicity in combinations can be avoided by giving drugs and radiation in sequence.

Radiosensitivity of normal tissue varies greatly among patients, so identifying those who can more safely receive higher doses is important. Developing predictors of who will suffer from side-effects from radiation is the subject of a European programme called Requite (see requite.eu) and also the Radiogenomics Consortium, set up in 2009, which has the specific goal of producing assays to predict risk of toxicities after radiation therapy, as outlined in a recent paper, 'Radiogenomics: radiobiology enters the era of big data and team science' (*Int J Rad Onc* 2014, 80:709-713).

Lambin is a proponent of decision support systems to aggregate data to help make such predictions (see *Cancer World* Sept–Oct 2013). While he backs the search for definite biomarkers, he sees biomarker data as part of the mix, mentioning for example work on mitochondrial DNA from saliva in lung cancer models combined with prediction models. He also stresses the field of radiomics, in which imaging data that quantifies differences in tumour intensity (a scale for describing radiodensity in CT scans), together with shape and texture, can have prognostic power (for more on this see *Nature Communications* 2014, doi:10.1038/ncomms5006).

But progress is slow. Bernier says that biomarkers have been extensively investigated to predict the outcome of almost all solid tumours exposed to radiation alone or radiation combined with systemic treatments. "So far, and in contrast with what has happened in medical oncology, it is clear that their clinical relevance remains disappointing in patients treated with radiation combined with chemotherapy or targeted agents. We must identify more powerful biomolecular markers if we want to intensify the role of personalised medicine in patients treated with radiotherapy."

There are notable exceptions. Bernier mentions HPV (human papillomavirus) status in oropharyngeal carcinomas, hypoxia levels in cervix cancer, and MGMT methylation status in patients with glioblastoma. The role of HPV is an ongoing research area – those who are HPV positive actually have a better outlook, and a recent study indicates that they may safely receive lower dose radiation after chemotherapy. The identification of patients with a 'silenced' MGMT DNA repair gene in glioblastoma has been an important advance in predicting response to treatment with temozolomide and radiation for patients with this high-grade brain tumour.

Latest research

At Heidelberg, Abdollahi and his group are now working on the underlying molecular mechanisms and response predictors of novel therapies, especially for the tumour–stroma 'microenvironment', including high-throughput techniques on the genome, proteome and so on, with anti-angiogenesis as a particular focus. "Tumours protect their vasculature from radiation- and chemotherapy-induced damage by releasing pro-angiogenic and pro-survival factors," he says. Immunotherapy is also a promising area, he adds.

Then there is also the proton and carbon ion work with the Heidelberg Ion-Beam Therapy Centre – overall, this is one of Germany's largest cancer research centres, with a substantial fraction of patients with head and neck cancers and gliomas, for instance, being treated in multimodal trials.

Certainly, genomic work is a promising area, as it is generally in oncology, and many groups are investigating predictive signatures and associations between radiosensitivity and genetic alterations. One group may have taken a lead – Javier Torres-Roca and team at the Moffitt Cancer Center in Florida has developed a signature that can predict radiosensitivity and, importantly, has been validated in breast, rectal and other cancers. Such work is not necessarily welcomed by some in the radiotherapy community who are paid for each treatment episode, as signatures can show who may avoid or receive less radiation.

Meanwhile, Lambin is not waiting for the big drug companies to come up with new agents. A bio-tech start-up from his clinic in Maastricht, DualT-Pharma, is developing a 'smart dual drug' that exploits the overproduction of acid in tumours. The drug targets cells with an inhibitor for a protein that regulates acid (called CA IX), thereby promoting more acid, which could kill

cancer cells, and also deploys a radiosensitiser to guide a radiation 'warhead' to the target.

Lambin also mentions immunotherapy combined with radiotherapy as one of the most important ways forward, suggesting it could extend treatment from locally advanced to the metastatic stages. When radiation causes cell death it also releases antigens that stimulate the immune system, which can be enhanced by drugs such as IL2 (interleukin 2), which is a class of drug known as a cytokine, but on its own is uncontrolled in the body and can have bad side-effects.

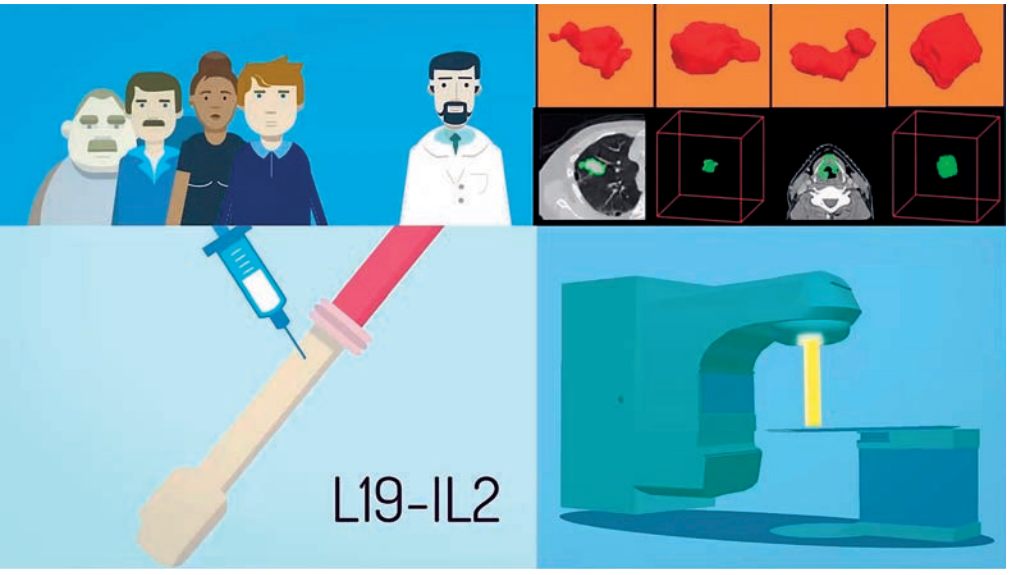
As an example of how to develop this type of immune response, Lambin and colleagues have used an immunocytokine consisting of IL2 coupled to an antibody that binds the combination to tumour vasculature to release cytotoxic T-cells, and they have shown a 75% cure rate in certain animal models. A phase I study has been approved, which will investigate patients with a low number of small metastases (fewer than five, a status known oligometastasis), in which they will receive high-dose radiotherapy and the combination drug, with the eventual aim of seeing if more metastases can be prevented. A study on radiation alone has already been carried out (*J Thorac Oncol* 2012, 7:1547–55).

Lambin says that oligometastasis is also proving to be an important condition just for treatment with stereotactic radiotherapy (which uses numerous precisely targeted beams). In fact a recent study (*Lancet Oncol* 2014, 15:387–395) on brain metastases suggests that treating up to ten sites may be at least as good as treating patients with two metastases, and probably better than whole-brain radiation – and that adding targeted therapy could be the next step.

Abdollahi also points out that the major differences in tumour type can influence the design of radiotherapy research. Much of the emphasis is on improving local control, where radiation has had much success in, say, breast and rectal cancer. However, aiming for similar local control, e.g. using dose escalation, in tumours where there is a high failure rate within two to three years, such as in glioblastoma or lung cancer, may not be appropriate.

That new approaches could be quite simple is also shown by yet another trial Lambin is involved with, which is using nitroglycerin to address hypoxia when treating non-small-cell lung cancer. Nitroglycerin improves blood flow but has not been studied with radiotherapy – so in a phase II trial 60 patients have been given a nitroglycerin patch during a radiotherapy course, with the effect on blood supply measured by dual energy CT and HX4 (a blood hypoxia imaging marker) PET scans.

Bernier is more down to earth about current prospects and considers much of the work is only just beginning. "The tumour micro-environment is an appealing target but we have no clear demonstration so far that it will have a clinical impact in the medium term.



MAASTRO CLINIC

An innovative strategy which combines high-dose radiation with an IL2 combination drug that binds to tumour vasculature has been approved for a phase I trials at the Maastro Clinic in The Netherlands. It is intended as a curative therapy for people with a small number of metastases. Animations of this and other novel treatment approaches developed at the Maastro Clinic can be seen on its YouTube channel – www.youtube.com/user/MaastroClinic/videos

"How to bypass radio-resistance in cancer stem cells is an interesting domain that we should explore more"

"An international consortium may be needed to speed radiation modifiers into clinical use"

How to by-pass radio-resistance in cancer stem cells is an interesting domain that we should undoubtedly explore more extensively.

"Immunology remains practically unexplored for its impact on radiation modulation, except in patients with non-Hodgkin's lymphoma who are benefiting now from radio-immunotherapy. And research on the radioprotection of normal tissues can still be considered in its infancy, as most attempts to deliver drugs to tissue next to the tumour and exposed to radiation have yielded inconclusive results."

The top three subjects for grants listed by an ASTRO task force reporting on biological science in radiotherapy as of November 2012 were tumour microenvironment, normal tissue and radiosensitisers, but despite all the promising work in these areas, little has made it into clinical practice (*Int J Radiation Oncol Biol Phys* 2014, 88:11e17).

Funding and organisation

In short, more work needs to be done before these sorts of novel approaches have a chance to make their way into the clinic. The question is where the capacity and funding to carry out that work will come from.

The ASTRO task force concedes that "radiation oncology is a relatively small specialty with a limited number of committed investigators and finite resources," while a paper on funding suggests that "the field of radiation oncology is underfunded by the NIH [US National Institutes of Health] and that the current level of support does not match the relevance of radiation oncology for cancer patients or the potential of its academic workforce" (*Int J Radiat Oncol Biol Phys* 2013, 86:234–240).

In fact, in fiscal year 2013, this paper reckons that radiation oncology research in the US received only 1.6% ($85.5 million) of the $5.4 billion in cancer research funding from the NIH, although as in Europe, it is not easy to measure exactly where funds are going and what all the sources are, given the diversity of the field, which takes in sectors such as medical physics and radiobiology.

A paper published last year in *Science Translational Medicine* (5:173sr2), on 'new paradigms and future challenges in radiation oncology', adds that "it is critical to widen the therapeutic window for radiotherapy at the biological level, particularly in situations where the physical and technical advances could be nearing a plateau… but we are left with the impression that there are many uncoordinated and competing research efforts."

Wider cooperation between groups would seem to be part of the answer. Lambin says Maastro is one of the European centres to have research tie-ups with several top North American groups such as Moffitt, Dana-Farber and UPenn. Heidelberg is part of a consortium with Tufts and Harvard, and Abdollahi says an important collaboration is about to start between the US National Cancer Institute and Germany's National Centre for Radiation Research in Oncology (NCRO), which combines the centres in Heidelberg and Dresden, to focus on translational research.

A paper published last year, 'Lessons learned from radiation oncology clinical trials', suggests that an international consortium may be needed to speed radiation modifiers into clinical use, as at present they are just too much of a "secondary path, spin-off, or occasional afterthought to drug development" (*Clin Cancer Res* 19:6089–6100). The Radiogenomics Consortium, as noted above, could be a model. It currently has more than 170 members from 90 institutions in 20 countries, but is making no promises yet.

There are some other encouraging signs of serious national investment in the sector. Sweden, for example last year announced a 'national test bed for innovative radiotherapy' via university hospital and industry collaboration. In the UK, the Radiotherapy–Drug Combinations Consortium (RaDCom) is another recent initiative. But generally Europe has a shortage of centres of excellence in oncology.

Given the high proportion of patients treated with radiotherapy, and the variety of promising areas of research being pursued, it's not surprising then that many leaders in the field feel their potential contribution to improving outcomes for cancer patients merits more than the estimated 1.6% of cancer research funds coming from the main US funding body.

Finding ways to get greater visibility for the many innovations in the field, and their implications for patients, will be important in winning the argument for the support they need. ■

Inside India's cancer epidemic

Epidemiologists have long been warning of the rapid rise in cancer rates hitting low- and middle-income countries. But it takes a journalist to get across how those statistics are playing out in people's lives. Jason Gale, who covers Asian Healthcare for *Bloomberg Markets*, received a Best Cancer Reporter Award for his piece on the cost of cancer in India, reprinted below.

Oncologist Bhawna Sirohi hurries to the front of a packed seminar room at Mumbai's Tata Memorial Hospital on a Thursday afternoon in April. Cramming this meeting into her 12-hour workday, she greets more than three dozen breast cancer patients united by the bright scarves covering their bald heads.

Sirohi says that when she began her job at Tata Memorial, Asia's largest cancer treatment center, last year, she realized she could never give the 50 to 60 patients she sees each day enough individual attention. Doctors at India's premier oncology hospital typically have less than 10 minutes apiece for 1,000 newcomers a week. They often examine three people at a time in a single room.

During Sirohi's 11 years at London's Royal Marsden hospital, she saw no more than 35 people a day and spent about 45 minutes with new patients. At Tata, she decided her best option was to co-host once-a-month group sessions for women coping with breast cancer.


Jason Gale

"In London, I would have a nurse holding the patient's hand, sitting with them, giving them a cup of tea," says Sirohi, 45, in her 8-foot-by-8-foot (2.4-meter-by-2.4-meter) office. Ten floors below, hundreds of people shift on metal seats, lean against walls or lie on the stone floor waiting for doctors.

"Here, they have been given devastating news; I deliver it at least seven times a day," she says of patients with terminal cancers for which there are no treatments. "Sometimes you do it for 23-year-olds, which is very tough."

Cancer is sweeping through India, taxing its doctors and stressing a health-care system already overburdened by some of the world's sickest people. The country is home to 17% of the global population but suffers from 21% of the disease burden, the

Bloomberg Markets

Against the odds: This is a story about a health service that is good at getting the most out of the limited resources it has, but is overwhelmed not just by rising numbers but by the unexplained high rates of more aggressive cancers and problems of late detection

Supplementary reporting was by Ketaki Gokhale and Bhuma Shrivastava. Photography by Shiho Fukada

SHIHO FUKADA

Families line up at Tata Memorial Hospital in Mumbai, India's premier cancer treatment center (*top*). Men register women for breast-related services (*below*)

World Health Organization says.

One person in India dies from cancer every 50 seconds. Hundreds of thousands more face surgery and years of treatment – driving a quarter of their households into poverty and making cancer the disease most likely to impoverish, according to the World Bank.

Breast cancer is gaining in alarming ways. A decade ago, it moved ahead of oral cancer, in which India ranks no.1 worldwide, to become the country's fastest-growing malignant disease.

India will lose $20 billion in economic output from 2012 to 2030 as a result of breast cancer, the Harvard School of Public Health in Boston projects.

Survival rate

More than 115,000 new cases are diagnosed each year. The few treatment centers that track survival say 52% of breast cancer patients in India are alive after five years, a 2010 study published in *The Lancet* found. That pales in comparison with the 89% survival rate in the US and the 82% rate in China.

"The growing cancer burden threatens to overwhelm health systems and budgets in the developing world," WHO Director General Margaret Chan told the organization's International Agency for Research on Cancer in Lyon, France, on February 4 [2013].

Globally, cancer emerged as the no. 1 killer in 2010, when it passed ischemic heart disease. Today, it ends more lives than AIDS, malaria and tuberculosis combined. The economic toll: $1.16 trillion annually, or 1.6% of global gross domestic product.

Developing countries such as India face the brunt of the incursion. They report more than half of new cancer cases and two-thirds of deaths, compared with 15% of cases in 1970. At the same time, only 5% of global spending on cancer occurs in low- and middle-income countries, Harvard University researchers wrote in *The Lancet* in 2010.

'Explosive change'

"It is an explosive change," says Benjamin O. Anderson, a surgeon at Seattle's Fred Hutchinson Cancer Research Center and chairman of

Oncologist Bhawna Sirohi discusses treatment at Tata Memorial, which saw almost 60,000 patients last year

the Breast Health Global Initiative, which provides guidelines for low- and middle-income countries. "The bomb already went off, and now the question is, how do we handle it?"

India can ill afford the rising number of cancer cases. Asia's third-largest economy is contending with the slowest pace of growth in a decade – 5% in the year ended on March 31 [2013]. Foreign investors who have buoyed the nation are pulling money from Indian securities.

The country's vaunted success in lifting 137 million people out of poverty may stall – a victim of spiraling costs and families who lose breadwinners as they battle cancer and other chronic diseases, says Srinath Reddy, president of the Public Health Foundation of India.

Spurning treatment

"Many people will not even be able to afford care and will forgo care," says Vikram Rajan, a doctor and senior health specialist at the World Bank in New Delhi. "We cannot wait another 10 years to look at this problem. We have to look at this problem now."

Even before the cancer scourge, India's $65 billion health-care system was struggling to keep up: more than 300,000 babies each year fail to live beyond their first day, and one in 170 women die in childbirth or from pregnancy complications, according to Save the Children, which works to protect young people. India accounted for three of every five new leprosy cases in 2012 and a quarter of tuberculosis sufferers.

Now, cancer is exploding as more Indians live into their mid-60s, up from an average life expectancy of 50 before 1970. At the same time, the country is still battling such traditional killers as malaria and cholera.

Fresh threat

"We haven't gotten over the infectious diseases yet, but the non-communicable ones are already on us," says Harmala Gupta, who founded New Delhi-based CanSupport, a charity that has provided free medical services and support to more than 50,000 cancer patients.

Gupta, who herself beat a blood cancer called Hodgkin's lymphoma more than 25 years ago, says breast cancer patients face special challenges.

Cultural taboos make many Indian women embarrassed to talk about their bodies. Held back by modesty, poverty or ignorance, they delay doctor visits when they find something wrong with their breasts.

When they finally get a checkup, their prognosis is often dire: in a third of cases, the tumor has spread to the skin or chest wall, making treatment less successful.

The lack of privacy at Indian hospitals exacerbates the problem. Gupta, 60, recalls the scene at a breast cancer clinic in a New Delhi public hospital in the mid-1990s.

Women humiliated

"They were asking women to disrobe, and they were palpating their breasts," she says. "It was supposed to be cordoned off by curtains, but the curtains had frayed. Everyone was sitting there and watching these women. You could tell on their faces the humiliation."

Indians with cancer are stigmatized, Gupta says.

"No one wants to talk about it," she says. "They're worried their children won't get married because of arranged marriages in this country. People think it's in the family. Children are taught to lie to their prospective marriage partners."

Mumbai homemaker Deepti Shinde says she ignored swelling in her right breast, hoping the pain would go away. In October 2011, when she finally mustered the courage at age 47 to get the first breast exam of her life, the tumor that had formed in a milk duct was the size of a lime and had invaded nearby lymph nodes. Her only option for survival was a mastectomy, which she underwent in January 2012.

"I got really scared," says Shinde, who quit school in 10th grade to work as a nanny and today shares a 10-foot-by-10-foot room and loft with her husband, 17-year-old son and five other relatives. "I didn't know a whole lot about cancer at the time. I wondered if I would live."

Shinde also worried about paying for surgery. Her doctor first referred her to a private hospital, where she was told the operation would cost 120,000 rupees ($1,950). The bill would have equated to almost a year's

income for her husband, a polio survivor who can work only part time as an electrician, and her brother-in-law, a laborer. She turned to Tata Memorial, where her mastectomy and two-night stay cost 5,000 rupees.

After the surgery, Shinde traveled to Tata from central Mumbai at least once a week for almost nine months. She arrived at 8 a.m. for 10 minutes of treatment. She never made it home until late afternoon.

"I used to just sit there, repeating God's name," she says of her six- to seven-hour waits. "It would feel like the day was never going to end."

Shinde's brother-in-law footed the bills for surgery and follow-up visits. A friend gave her money to help pay for chemotherapy, which she says cost 2,500 rupees per dose.

"Everybody in my family took care of me when I was sick," Shinde says. "But it was hard on my family in terms of money."

Cheaper drugs

India's government is helping patients manage costs by allowing companies to make cheaper, generic cancer-fighting drugs. The Ministry of Health and Family Welfare has sought so-called compulsory licenses for versions of Bristol-Myers Squibb Co.'s Sprycel for chronic myeloid leukemia and Ixempra for breast cancer as well as Roche Holding AG's breast cancer therapy Herceptin.

Roche introduced a lower-cost Herceptin packaged by a local pharmaceutical firm for the Indian market in August 2012. Natco Pharma Ltd. got government permission to make a cheaper copy of Nexavar, Bayer AG and Onyx Pharmaceuticals Inc.'s patented treatment for advanced kidney and liver cancer.

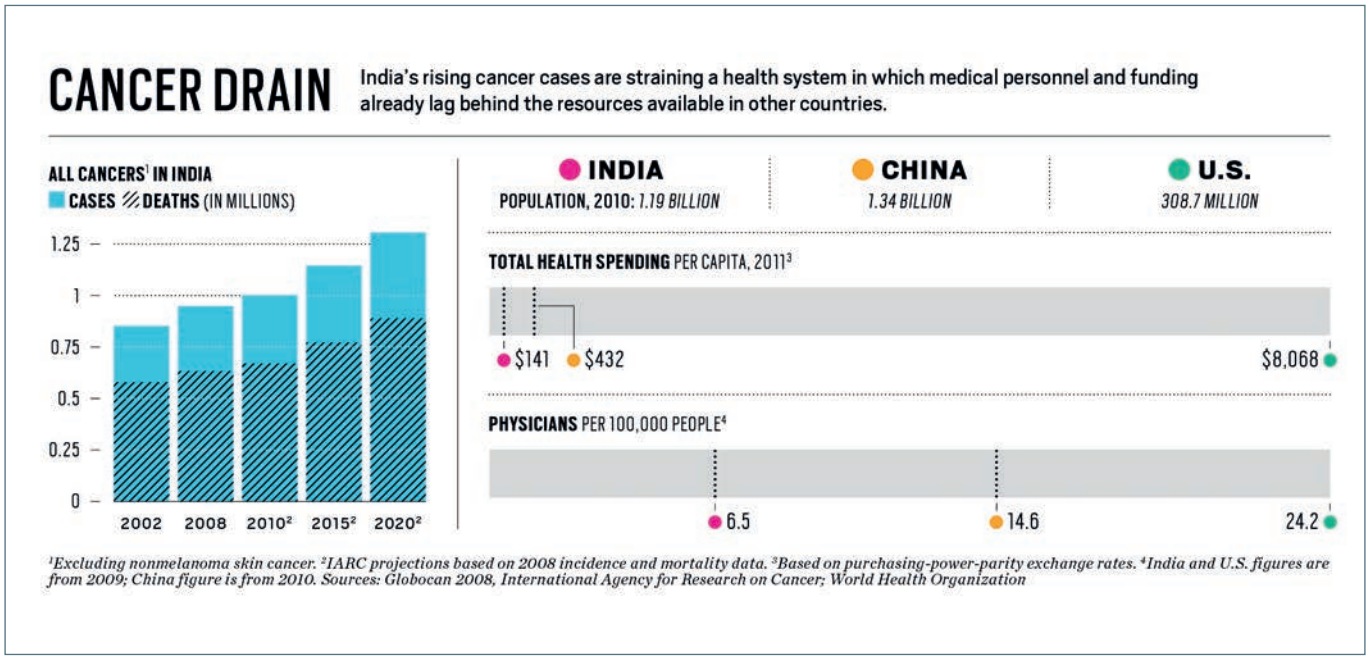
World Trade Organization rules allow such licenses to improve access to important medicines. The US, European Union and most of those regions' drugmakers don't like them. They lose money because they can't sell the higher-priced versions of the drugs, which are protected by patents.

Unique features

Researchers are trying to unravel why breast cancer is rising in India – and why certain features there differ from elsewhere. Half of the cases can't be explained by known risks, India's Council of Medical Research found in a 2005 report.

The WHO links breast cancer to such choices as having no children, having children late in life, not breast-feeding, excessive weight gain and frequent alcohol consumption – practices often found in westernized lifestyles. In India, these potential triggers aren't as common, and in many instances don't exist at all.

"All the risk factors that have been identified in the West don't seem to be operating here," Gupta says.



"These are women who have breast-fed their child. They marry early. Despite that, we are seeing this, and in younger women."

Younger women

In India, breast cancer typically strikes women at age 45 to 50 – more than a decade earlier than in the West. Fewer cases in India involve protein molecules targeted by estrogen, the female hormone that stimulates breast cell division.

In about 45% of Indian cases, breast cancer cells possess receptors for estrogen. That compares with about 60 to 65% of cases in Western countries, says Rengaswamy Sankaranarayanan, the IARC's head of early prevention and detection.

Doctors are interested in the estrogen receptor because it identifies women with a typically slower-growing disease who will benefit from hormone-based treatment, Sankaranarayanan says. The absence of estrogen receptors in a greater percentage of Indian cases means proportionally fewer women will respond to hormone therapy.

"These are tumors that are likely to grow faster," Sankaranarayanan says. Some doctors say rising obesity may be stoking the breast cancer increase. Obesity may boost levels of insulin and another hormone called insulin-like growth factor 1, which causes insulin resistance and may promote cancer development, according to the National Cancer Institute in Bethesda, Maryland. Yet colorectal and kidney cancers, which obesity also spurs, aren't increasing significantly in India.

Cases like that of Mumbai resident Geeta Ambre, who has been afflicted with both breast cancer and Type 2 diabetes, may provide clues to possible links between the diseases. She was diagnosed with diabetes in 2001, when she was 40, and discovered a breast lump in 2011 as she was turning 50. Ambre had the lump checked out at Tata, where, she says, doctors put her mind at ease.

"I was scared and also too embarrassed to show it to anybody," recalls Ambre, 53, who had never had a routine annual checkup or gynecological exam, even though she's diabetic. Doctors found a fast-growing, grape-sized tumor that had spread to her lymph nodes. She had surgery to remove the lump in March 2011.

More aggressive

Sirohi, the Tata oncologist, helped supervise Ambre's chemotherapy and sees her in the support group. She says Ambre's tumor tested positive for a protein called human epidermal growth factor receptor 2, or HER2.

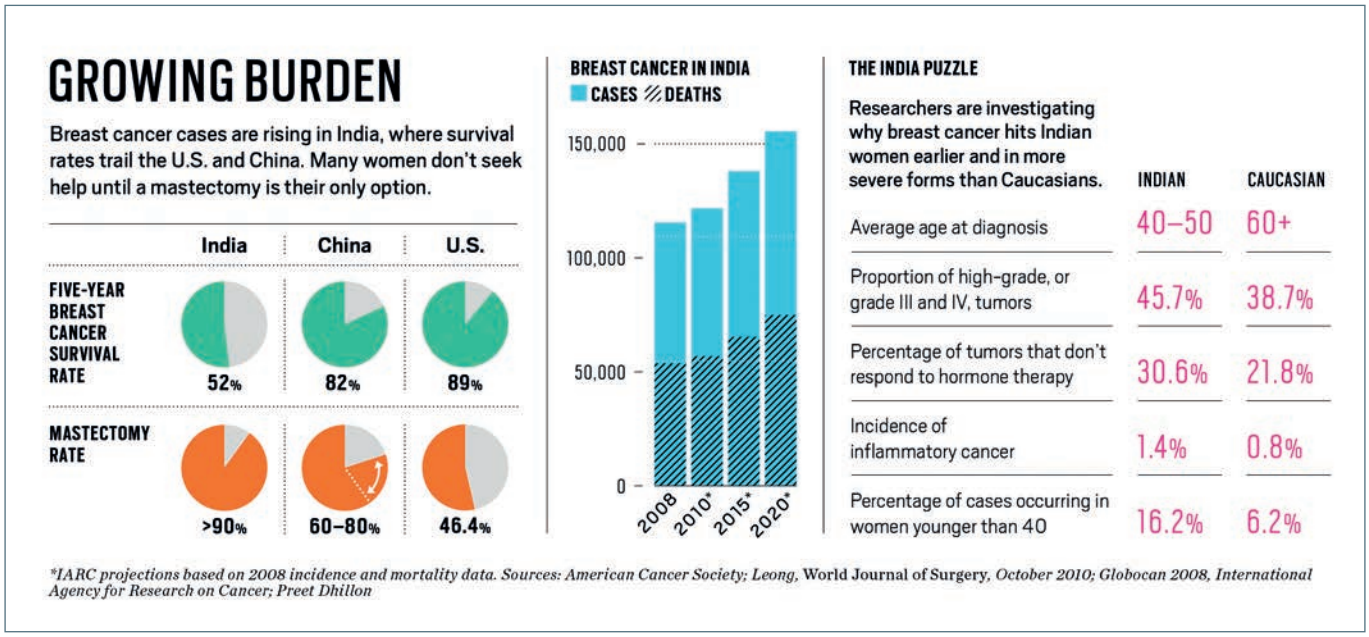
Cancers with this mutation tend to be more aggressive, and doctors speculate it may be more common in breast cancer patients in their 20s and 30s.

Preet Dhillon says researchers can learn a lot from Ambre and others with diabetes lurking in the background. An epidemiologist at the Public Health Foundation of India in New Delhi, Dhillon has been studying cancer patterns for six years.

She says if scientists can disentangle the mechanisms and disease-causing pathways that stem from body fat, insulin resistance and inflammation, they may find both diseases share the same cause in some cases.

Like breast cancer, diabetes typically turns up a decade earlier in Indians than in Caucasians. As many as 14% of urban Indian women have diabetes today, up from about 3% in 1972.

Breast cancer survivors attend a monthly support meeting that Sirohi co-hosts at Tata



IARC projections based on 2008 incidence and mortality data. Sources: American Cancer Society; Leong, World Journal of Surgery, October 2010; Globocan 2008, International Agency for Research on Cancer; Preet Dhillon

"It's an avenue that needs to be explored, along with genetics and the environment, especially considering the burden of diabetes and associated syndromes," says Dhillon, an American of Indian heritage who received her doctoral training at the University of Washington and Fred Hutchinson Cancer Research Center in Seattle and first came to India through an IARC fellowship in 2003.

Rajesh Dikshit, the chief epidemiologist at Tata Memorial, is trying to crack India's breast cancer mysteries in a sixth-floor office that echoes with beeping horns from the street outside. He says many Indians die from cancer without ever being diagnosed, let alone treated.

Dikshit came to Tata six years ago after a two-year stint at the IARC in France and studies at Finland's University of Tampere, where he got a PhD. He is exploring why a small number of women develop breast cancer in their mid- to late 20s.

'Fastest growing'

"In the Mumbai population, breast cancer is the no. 1 fastest growing," Dikshit, 49, says. "There are many cases with women that are less than 35 years of age in India."

On this day in April, Dikshit pores over the blood-test results of 1,500 breast cancer patients and compares them with 1,500 women without the disease.

He's searching for 384 DNA patterns to identify the most-common variations to figure out the biological factors that increase susceptibility to breast cancer. He says the research will reveal how changes in a woman's body mass affect breast cancer development and whether doctors can use abdominal fat to predict risk.

Diabetes, heart disease and certain cancers are all linked to inflammation and the damage it causes, suggesting possible unifying drivers, he says. His findings on common genetic variations in breast tumors should be ready for submission to a scientific journal in early 2014, he says.

Dikshit is also looking for differences in nutrition and body mass in about 2,500 patients from urban and rural areas. He wants to compare them with about 2,000 women who don't have breast cancer.

This study will identify whether young, rural women are at a higher peril of so-called triple-negative breast cancer, an aggressive form that doesn't respond to three main drug therapies.

"It's quite possible that the first 20 years of life are more important than their recent residential status," he says.

Outside Dikshit's office, 10 women enter patient records into a database. The electronic records enable the hospital to calculate the percentage of patients alive five years after diagnosis and identify which treatments have been successful.

Such efforts show how Tata is working to get a handle on the flood of cancer cases. Last year, 59,184

Rajesh Dikshit, Tata's chief epidemiologist, analyzes patient data to try to crack the mysteries of breast cancer in India

patients filed through the 700-bed hospital; 23,019 were admitted for treatment. India's Department of Atomic Energy, which manages the hospital, deemed 60% of those treated too poor to pay for basic care – a cutoff usually set at a monthly income of 3,000 rupees [$40] or less.

Little privacy

The hospital's annual expenditure is $40 million, equal to $1,738 per hospitalized patient. People who can afford to pay are treated individually in a private wing.

The MD Anderson Cancer Center in Houston, by comparison, had net patient revenue of $2.96 billion from 26,726 admissions in the year ended on August 31, 2012. That's about $110,000 per hospitalized patient. For international clientele, Anderson provides a service that helps them decide what to pack.

Tata has no such luxuries. Government-subsidized patients usually share their first visit with two or more other people. At least three doctors discuss each new case – with everybody in the same room.

"The whole thing with patient confidentiality goes out the window," says Sirohi, who, in addition to seeing 50 to 60 patients a day, also indirectly oversees the care of 40 to 50 more. "The alternative is, they don't get the care at all."

Cobalt, vinegar

Anderson, the Seattle breast surgeon, sees a silver lining in India's handling of the overwhelming numbers: Tata has learned to make the most of what it has. For one thing, it relies on less-expensive technologies. Doctors use cobalt-powered units for radiotherapy, alongside more-expensive linear accelerators, and vinegar for cervical cancer screening instead of Pap tests.

"You look at this and think this is chaos, yet they're doing it," he says. "They really manage high volumes of patients with high-quality care."

Ambre, the patient with Type 2 diabetes, returns to Tata every six months for a checkup.

"My friends – I've told them to do breast self-exams, and they are all doing them," she says. "They were all scared by what happened to me, so now they keep checking themselves." None has found a lump, she says.

Shinde is cancer-free and in good health after her mastectomy in 2012. She attends Sirohi's meetings every month and in June began working an hour a day for a neighborhood moneylender.

"We are learning what to eat, what not to eat, how much to exercise," she says. "I feel good after coming here. It's possible to recover from this. What's there to be afraid of?"

Shinde and Ambre can count themselves among India's fortunate ones. Sirohi says she's frustrated every day by the cancer she sees and can only chip away at.

"My hands are, in a way, tied because I want to do so much," she says over breakfast at a Mumbai hotel. "You can't. I don't have the resources. People are so poor."

"You feel for every patient," she continues. "I want to fight for them because you are their best advocate – the only advocate." ■

This article was first published in *Bloomberg Markets* on December 2013 and is reprinted here with permission.

Age discrimination at a time of health rationing: unthinkable or common sense?

Last May, Karol Sikora, former director of cancer services at Hammersmith Hospital in West London, who led the WHO's cancer programme between 1997 and 1999, hit the headlines when he suggested that younger patients should have priority when it comes to accessing some of the very expensive new cancer drugs. We all have to die of something, he argued, and giving everyone the right to "stave off the evil hour of death" for as long as possible, no matter what the cost, is unsustainable.

His statement provoked some angry reactions.

Ciarán Devane, Chief Executive of Macmillan Cancer Support, spoke for many in the medical profession when he said: "We have a duty to treat people as individuals and assess them based on their fitness for treatment, not date of birth," and that to deny older cancer patients treatment based on their age alone is unacceptable discrimination. This is a view strongly endorsed by SIOG, the international organisation of oncologists specialising in treating elderly patients.

But is it really so unacceptable? With rationing of expensive treatments becoming the norm among European countries, should people struck with ill health at an earlier age be denied the therapies they need because health budgets cannot meet the huge demand – not least for cancer care – among people nearing the end of their expected lifespan?

Cancer World's Liz Bestic asked Ulrich Wedding, a specialist in geriatric oncology at Jena University Hospital in Germany and SIOG board member, to discuss the issues with Karol Sikora to see whether they could find common ground.

Every healthcare system in the world is struggling to contain the rising costs of cancer care. None can do everything for everybody so we have to have priorities. That may mean limiting access to some very expensive life-extending cancer drugs on the grounds of age as well as other factors.

Prioritisation can involve several factors: the quality of life of the patient, the likelihood that the drug will be successful, the relative stage of the cancer, and how many previous treatments have been given.

Oncologists have always taken these factors into account. The problem now is huge escalation in the costs of drugs for only months or weeks of survival benefit. Over the past decade we have seen the monthly cost of a box of cancer pills escalate from a few pounds to over £8,000.

So we have to be sensible.

Karol Sikora

Ulrich Wedding

It is not justified to look at the cost of cancer care separate from other healthcare costs. Even healthcare costs should not be looked at separately from other public spending. The topic comes up because, as you say, the cancer drugs are very expensive.

However, when looking at older cancer patients, chronological age is not always a good criterion for decision making. If you compare a group of let's say 70- to 80-year-old patients, they are a very heterogeneous group. Some are very fit and independent in their daily lives. They travel around and even care for other people. Others have very poor health status with chronic diseases and need of social support.

To say the life of a 90-year-old woman is not as worthwhile as that of a 30-year-old breast cancer patient should not be part of the oncologist's thinking. Otherwise oncologists are playing God. It should not be their decision that the additional year for the 90-year-old is not as worthwhile as for a 30-year-old.

I also believe that when a drug is approved it should be possible for all patients with a good risk–benefit ratio to receive that drug. It should not be a decision made at the bedside by oncologists. The oncologist has to decide on the risk not the value of the benefit.

You simply can't dilute out the problem by involving other sectors in healthcare. If we, as oncologists, have been tasked with finding a solution for cancer, then I believe that age should come into it. Of course biological age as well as quality of life and its productivity need to be factored in as well. Chronological age is well defined – the other criteria are less so, and so must involve value judgements, which are of course subjective.

I agree with you that the expected level of clinical benefit has to be factored into the equation whether or not to give a high-cost cancer drug, whatever the patient's age. But I do believe that we should give younger patients more options in the form of different lines of treatment compared with older cancer patients, and this is common practice in most countries. The real problem is that we have no idea how effective a drug will be until we give it.

Oncologists ration drugs all the time by age anyway. Interestingly if you go to most middle-income countries where healthcare is not completely free, patients too are

much more savvy about the relative values of prolonging life at great cost.

Rationing is inevitable, and we have to decide how to do it in the fairest way. I still think age is one of the factors that needs to be considered, along with comorbidities as you suggest. On the whole these come with age of course. And nowadays individuals can circumvent government or insurer rationing simply by paying for the drug if they have the resources. That's the way a free market works whether we like it or not.

I don't believe the free market can apply here because we're talking about healthcare. The patient is not a customer who can simply buy the drugs he wants to have. In Germany you certainly cannot buy a drug from another country and use it over here. A medical system is different because the doctor has to decide if the drug is going to be of benefit to the patient.

Only if there is a likelihood of medical benefit of receiving a certain drug is it important to know whether the patient wants the drug or not. The use of any drug should be supported by the likelihood of benefit not simply the availability of the drug.

Whether or not we make a decision to treat younger patients as opposed to older needs to be looked at case by case. The younger patient may be justified if the benefit is greater for them. So if you have a 30-year-old who is already on a fourth-line treatment compared to an 80-year-old on their first treatment the older patient may get more benefit.

I'm afraid the free market is very much alive and kicking and the reality is that a drug is a market commodity. The price of a box of pills cannot be different because of different response rates in different people. A new car is the same price even though some break down after three or four years. You don't get your money back. In free markets, commodities are purchased where they are cheapest and with internet pharmacies there are no borders any more.

Comorbidities and functional status are all relative. I have a delightful 80-year-old lady with widespread bone metastases who walks five miles a day to get her shopping. She is failing on capecitabine, having already had FEC and docetaxel. So should I start her on a fourth line of chemotherapy? We know her gain from this is likely to be small. So if drugs have to be rationed, and they do, then surely people who are likely to live for a long time should get priority? So that means the young should be higher up in the pecking order than the old.

Perhaps this should be a question for society as a whole? Should oncologists really have to take into account the price of the drug when they make their bed to bed decisions or should it be something which is decided by society? Who decides whether it is worth-

while to invest something like €50,000 for one year of additional life? In the UK NICE takes this into account when deciding on drug approval, but it is very different in each country in Europe.

In Germany there is a new system which has been introduced to decide whether a new drug implies a substantial improvement in the patient care, and that is when a higher price is justified. If there is only a small benefit or no additional benefit, the price the company can get for the drug is much smaller. I think there needs to be more pressure on the companies to have more affordable drugs.

But we need also to guard against ageism here. Older people are under-represented in most clinical trials and so we need more studies particularly those which focus on older patients where there is very little data. There is plenty of evidence out there that older patients are very keen to participate in randomised controlled trials if they are offered, which is why we try to encourage older patients to take part in our research.

These studies are vital so that patients can make more informed decisions. We need to be able to say openly and honestly there are no data that says you will benefit from this treatment so that no treatments are given simply based on the wishes of a patient.

You are right– the patient has to have all the information to make an informed choice, and increasingly there is a general move away from the 'doctor knows best' approach into a much more collaborative approach with the patient.

So I am not advocating an age cut-off for expensive cancer drugs. But age, and more importantly quality of life, are the criteria which need to be factored into the decision to treat actively or to provide best supportive care.

There is no magic age, but there are a whole series of things that come into consideration. We do it anyway, despite the fact that in our NHS there is a total anti-ageist policy. Many of the decisions that are made are not because the patient wouldn't tolerate it, but because the benefit is so small even if it's successful.

I believe that cancer drug rationing is now inevitable in all health economies. Even the richest systems in Europe and the US cannot support that, and it is a huge crisis.

It's now time to be explicit. This seems only fair when the value of giving £100,000 of cancer drug is bound to have much greater potential benefit in someone whose life expectancy is 40 years rather than five.

We have all got to die some time, but we are afraid of looking at death. Death is inevitable. So we need to be more honest and open with patients about their chances of survival. Oncologists are often afraid to speak about their own limits of the treatment, and perhaps need to be more open about saying that chemotherapy will not help. Patients also need to be aware and not have their expectations raised.

When I talk to my patients I often say it's no problem to give you another infusion of chemotherapy. We can do that and often do. But the really difficult decision is whether you benefit from that treatment. The patient sometimes has to understand that the better decision is to do nothing. Even though they may have a limited lifespan they can enjoy it without having to go through more gruelling therapy.

Mindfulness

a way to live life in the present tense

PETER MCINTYRE

> "I have learned to shift from seeing myself as invulnerable to quite vulnerable – and to know that as not something to push away. There are good things about vulnerability. I have never felt so loved, supported, treasured... and have come to know some people in a way I think I never would otherwise."

These were the words of June Robson one month after being diagnosed with an osteosarcoma. She was at first told this was "too large to remove", but had surgery following a second opinion. She had time to think about how her life had turned upside down after her first dose of chemotherapy as an inpatient in Christie Hospital, Manchester, in northern England.

"I had fallen out with my body big time, to the point that I found it hard to look at myself in a mirror. What's more, I now suddenly noticed that I used to really like my body. I've had the luxury of almost never being ill, being pretty fit for a young 60-something, and having a body that let me do pretty much anything I wanted. What things I had taken for granted!"

When first diagnosed, June was in a state of something close to panic. What helped her to cope with the psychological challenges was a technique for dealing with the reality of here and now rather than fearing for the future – the technique of mindfulness.

Mindfulness is currently suffering the curse of fashionable celebrity – presented as a kind of "chilling out", which is more or less the opposite of what it is. Even the normally serious *Financial Times* ran a feature this September on "mindfulness" for home interiors. ("To turn on a light mindfully means being thoroughly caught up in what you are doing.")

The psychological impact of cancer diagnosis and treatment is as far from this self-indulgent selfie 'me-time' as it is possible to get.

As June, now six months out of treatment, says: "My sarcoma had every bad news label attached to it apart from metastases. I am anxious when I go for follow up. When I went on holiday I was convinced something would go wrong when I was out of the country. I also have pain from the surgery – different amounts of pain on different days, but I am never pain-free."

On the whole June is a fan of "good old-fashioned western medicine", but she trained to teach mindfulness for people with chronic pain and brain injury when she was working as a psychologist in the NHS, before she had cancer. "It helps with letting go of all that wishing and hoping that things were different, that people spend their time and energy on." It also helps to prevent the brain from endlessly

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"ruminating" on what caused the disease or the worst that might happen.

Applying it herself was instructive. "It helps with the two disabilities I have been left with – hearing loss and getting about on crutches. When the wretched crutches are really irritating, mindfulness brings you back."

Focusing on what matters

Suzie H from London is in her 40s and was diagnosed two years ago with a uterine leiomyosarcoma that grew to the size of a small baby. She has faced three major operations including a radical hysterectomy and removal of ovaries and two rounds of chemotherapy. She puts her feelings more strongly. "It really is a bloody journey through all of this; it is treatment and life and death and looking forward and looking back. You can't stop yourself.

"I want to confront the issues of illness. I am more afraid of getting really ill again and being in this awful state of illness than I am of dying. But I also have to confront the fact that I might die – cancer can be very fast moving."

Suzie attended a mindfulness course at the Penny Brohn Cancer Centre in Bristol. "I do it when I notice my head is racing into the future and I am becoming fearful of things that might happen, and when I recognise that I am worrying about something I cannot control. I try to make myself present. I will take some deep breaths. I might be walking around or I might go and sit down or lie down and concentrate or meditate."

For Suzie, mindfulness means focusing on what matters. "In our modern society there is some glorification of being busy all the time and rushing around. Everybody could do with pulling themselves into the present and stop worrying about what might happen in the future or has happened in the past and truly enjoy the moment you are in right now. It is really important to be present in our lives."

Mindfulness-Based Stress Reduction (MBSR) was developed in the USA by Jon Kabat-Zinn out of the Buddhist practice of 'sati' (presence of mind), and has been adapted as Mindfulness-Based Cognitive Therapy (MBCT) for people with depression. Both have been used by cancer patients.

MBCT specifically for people with cancer (MBCT-Ca) was developed by Trish Bartley, one of the founding

"Turning towards anxiety about what is going to happen to your children if you die – that is not pleasant"

teachers at the Centre for Mindfulness Research and Practice in Bangor University, North Wales. She ran the first course in 2001 soon after she completed treatment for her own breast cancer. It continues to run three times a year at North Wales regional oncology units and around the UK – as a weekly class over eight weeks with a commitment to daily practice at home.

According to Bartley, the psychological impact of cancer can be even more difficult for some people than the physical disease. Cancer patients may deal with psychological trauma or distress by avoidance (pushing away unwanted experiences) or by rumination (caught in loops of negative thinking). The aim of the course is to help participants come back to the present experience and in time 'turn gently towards' what is happening with some level of kindness to themselves.

Bartley says: "Patients coming on a course are seeking some kind of release from their suffering. Many are desperately anxious, some are depressed or a number have been traumatised by their experience.

"If they benefit from the course, a participant no longer tightens around the anxiety or pushes it away, but is able to sit alongside it and breathe into it with a bit more kindness."

Mindfulness also offers an opportunity to appreciate life more. "Because this is about being present to experience, we have more possibility of noticing and enjoying what is around us. You are more likely to see the robin on the fence, or that the sky is a lovely blue or to feel the breeze on your face. The practice of mindfulness is to come back to your sensory experience. It might be a touch on the skin or a smell."

The course involves hard work and a commitment to practice, including daily exercises such as a 'body scan', focusing on parts of the body in turn to notice what is happening. Some people call this 'exercising the attentional muscle' – rather like going to the gym to improve fitness, flexibility and stamina, but in this case training the mind.

Bartley says that this is not about trying to make everything lovely or change the experience, but simply to notice what is there and bring the mind back when it starts to wander. "When our mind wanders, we move into 'automatic', where habitual reactive patterns happen. And that is where all those horrible, negative, difficult thoughts are lurking: 'This is my fault; I should have gone to the doctor earlier,' or 'Someone said something – she really meant that things are going badly'."

Patients may be at their most vulnerable when their treatment is over and they lose the everyday support and reassurance from their health professionals. This may be the best time to start the course says Bartley.

"People quickly go back into work or if they are retired pick up on what they did before, looking after the grandkids or whatever, but are still recovering from the effects of radiotherapy or chemotherapy or ongoing treatment. They often find they have not got the same energy, the same motivation. Friends and family congratulate them on 'getting back to normal', but the fears remain."

There is growing evidence for the efficacy of mindful-based cognitive therapy in dealing with the psychological impact of a cancer diagnosis and treatment, but Bartley makes no claims for it extending life. "Cognitive therapy and counselling and mindfulness are undoubtedly going to reduce the psychological burden, but in terms of the actual life/death outcome I don't think there is any evidence that a better psychological approach will improve your chances of living longer."

No quick fix

She absolutely rejects mindfulness as a middle-class 'me-time' lifestyle choice. "It is just too easy to see mindfulness as some kind of flaky quick fix, 'let's all lie down and relax and be happy'. Mindfulness is a really gutsy approach to working with difficulty. It needs a lot of courage and intention and persistence and support. The four movements of mindfulness: intention, coming back, turning towards and kindness, are very profound and not to be learned in five minutes. Turning towards anxiety about what is going to happen to your children if you die, my goodness that is not pleasant.

"I have taught people across the socioeconomic spectrum in a rural and in some ways disadvantaged area of North Wales. People come feeling miserable, not sleeping, and waking at night with awful ruminations. They cry

Head-dress (duality): Suzie H created this self-portrait after going through chemotherapy following cancer surgery; using mindfulness to stop herself continually dwelling on bad things that might happen helps her stay engaged with the good things in her life

SUZUKIEHOWITZER.COM

very easily or their mood is dipping to the point where it is hard sometimes to get out of the house. People come because they want to feel better."

Marguerite Wallis, who teaches people with chronic disease in Oxford agrees that "mindfulness is not zoning out, it is zoning in." She sees it as a non-judgemental, loving kind consciousness of the present moment. "Often people's thoughts go crazy because there is an underlying feeling that 'This should not be happening to me.' You are beating yourself up and miserable because you can't do what you want, or you are running from yourself, keeping busy, getting exhausted, running on adrenalin or indiscriminate use of pain killers."

Not all cancer patients practise mindfulness in the same way. Jean had half of her left lung removed after being diagnosed with bronchiolo-alveolar carcinoma in 2010, and had a bad time because of subsequent pain, infection and weight loss. "I was coughing up blood and I lost six stone while on steroids. I was being referred from one 'ologist' to another without getting answers. You cannot imagine how scary this gets."

It was two years before she even saw a cancer nurse specialist and counsellor through a cancer support network and was introduced to mindfulness.

Always a strong swimmer, Jean went back into the pool to build up her strength and to raise money for lung cancer research. She used mindfulness to keep her thoughts from straying and found the barriers to how far she could swim melting away.

"When our mind wanders, we move into 'automatic'... where all those horrible, negative, difficult thoughts are lurking"

"I have found the swimming incredibly soothing – it energises me although it is a physical effort. I count the strokes and I am far more aware of what I am doing with my legs or arms and my breathing. Because of mindfulness and the concentration I have been able to break through most people's barrier. Each time I thought I could not do more, I just think I will push it another ten." She sometimes swims more than 300 lengths at a stretch raising money for the Roy Castle Foundation.

As a patient advocate Jean has now put mindfulness on the agenda of her local NHS Clinical Commissioning Group.

North America leads Europe in coverage. Linda Carlson has established Mindfulness-Based Stress Reduction courses at the Tom Baker Cancer Centre in Alberta, Canada, where she is director of research. In Europe, mindfulness for cancer patients is delivered in Cork and Dublin in Ireland, and is increasingly popular in The Netherlands. Trish Bartley's course book is being translated into Spanish, French and Italian, and being adapted for use in Iran and India. She teaches courses in The Netherlands, Portugal, Belgium and Switzerland.

However, most cancer patients in Europe are never offered it. Trish Bartley would like to see referrals from general practitioners and through cancer centres: "It would be great if it was offered quite close to where they access support and treatment, because that would mean it was most likely to be picked up and known about, both by the professionals and by the patients. To get mindfulness into some sort of training in oncology and palliative care would be amazing and incredibly useful."

She and colleagues in Bangor and North West England are looking at setting up "low-dose" mindfulness courses for staff in hospices, to help them with their own stress and potentially to benefit patients who may be nearing the end of life.

Sarah Bell, consultant in Palliative Medicine at the Garden House Hospice in Hertfordshire, England, is working with a colleague at Cambridge University to identify what research has been done on mindfulness in the hospice settings and has found very little outside North America. She supports the idea of shorter courses for patients and staff. However, those who fund services want to see evidence of effectiveness.

"Mindfulness in some guise in a modified course could be extremely useful for our patients receiving palliative care, and could be used in various forms, but there is no evidence that people are really using it and what we really need to do as a speciality is to start writing up what we are doing and try to get some evidence that it is benefiting our patients." ■

DEVELOPING THE EVIDENCE

The impact of mindfulness-based therapies on people with cancer is attracting a lot of research interest, but the evidence base is still quite limited.

- In 2013, the MINDSET trial led by Linda Carlson at the University of Calgary randomised 271 distressed survivors of breast cancer for mindfulness-based cancer recovery (MBCR), supportive-expressive group therapy (SET), or normal follow up (control group). Women who undertook MBCR showed the greatest reduction in stress symptoms and best quality of life. The women undertaking MBCR and SET both showed more stable cortisol levels than the control group. Researchers called for more investigation into the clinical implications (*JCO* 2013, 31:3119–26).
- The Australian National Health and Medical Research Council is funding a multi-centre trial of 190 men with metastatic prostate cancer who will receive mindfulness-based cognitive therapy or patient education to see the effect on levels of anxiety, depression and distress, quality of life and patient perceptions of outcomes (*BMC Cancer* 2013, 13:89).
- A 2013 review of studies conducted in November 2011 concluded that mindfulness-based stress reduction practice "shows a moderate to large positive effect size on the mental health of breast cancer patients and warrants further systematic investigation" (*Psycho-oncology* 22:1457–65).
- A 2011 review concluded "Mindfulness approaches are a promising intervention in cancer care, potentially across the cancer trajectory." Researchers recommended further research into different styles of mindfulness delivery (*Psycho-oncology* 20:681–697).
- In a 2010 study at the Helen Dowling Institute in Utrecht, The Netherlands, cancer survivors who undertook mindfulness-based cognitive group therapy showed significant improvements in fatigue and well-being (but not in functional impairment) compared with a control group (*Psycho-oncology* 21:264–272).
- A 2010 study from Australia of 115 cancer patients randomised to mindfulness-based cognitive therapy or a waiting list reported "clinically meaningful change" in depression, anxiety and distress (*J Consult Clin Psychol* 78:72–79).

Treatment of skin rash and pruritus induced by biological therapies

Skin rash and itchy skin are known to be common side-effects in patients treated with EGFR and tyrosine kinase inhibitors, and can be distressing, particularly when severe. A growing understanding of why this happens is leading to new ways of managing the problem.

Pruritus, more commonly known as itchy skin, is an increasingly important issue in cancer, as a growing number of anti-cancer drugs can induce this reaction. Rash and pruritus are very common with EGFR inhibitor- and tyrosine kinase inhibitor- (TKI-) based treatments, occurring in around 10–80% of patients. The rash typically resembles acne or occurs as red papulopustules. It is dose-dependent and can affect all areas of the face and body, typically peaking between two and four weeks after the start of treatment. Bacterial, viral and fungal infections are all potential complications of skin toxicities with EGFR and tyrosine kinase inhibitors.

Skin toxicity is graded from mild to severe. In mild skin toxicity, lesions are generally localised. Lesions are generalised in moderate skin toxicity, but the symptoms are mild. Patients with severe skin toxicity have generalised lesions and very severe symptoms. Severe pruritus and skin rash can have a serious negative impact

European School of Oncology e-oncoreview

The European School of Oncology webcasts monthly e-oncoreviews, in addition to its fortnightly e-grandrounds. These offer comprehensive overviews of specific topics, giving participants the chance to pose questions during the live webcast.

In this issue of *Cancer World* we publish an e-oncoreview presented by Daniele Santini from the Campus Bio-Medico, in Rome. He reviews the incidence, pathophysiology and management of pruritus in patients treated with targeted cancer therapies, and presents data on the use of aprepitant. Fausto Roila, from Azienda Ospedaliera Santa Maria, Terni, Italy, poses questions asked by the audience. Edited by Susan Mayor.

This e-oncoreview was sponsored by Helsinn

on quality of life in these patients.

The incidence of skin rash varies between different biological therapies (see p46). For example, the incidence of grade 3–4 skin rash with cetuximab is 5–18%, while it is 10% with panitumumab and 3–10% with erlotinib. The incidence of pruritus, as recorded in pivotal phase III trials, also varies between different EGFR and tyrosine kinase inhibitors – from 4–16% with cetuximab to a very high incidence of 57% with panitumumab. However, I think that the most important TKI for inducing pruritus is erlotinib.

In a very interesting meta-analysis published last year, Mario Lacouture's group demonstrated that all grades of pruritus are significantly increased with targeted cancer therapies compared with placebo (*J Am Acad Dermatol* 2013, 69:708–720). This meta-analysis demonstrates that patients treated with TKIs or EGFR therapies experience pruritus in their daily lives,

Pathophysiology of pruritus with targeted therapies

We know that substance P is one of the major neuromediators of pruritus. It binds to neurokinin receptors (NKR) 1, 2 and 3, but mainly to NKR-1, and represents a prominent activator of mast cells. NKR-1 is a G protein-coupled receptor localised not only in mast cells but also in the central and peripheral nervous system. It is also expressed by inflammatory cells. Substance P activates mast cells through NKR-1 and causes the release of pruritogens.

Biologic therapy with EGFR/TK inhibitors induces the secretion of stem cell factors and the subsequent accumulation of dermal mast cells in the skin of patients with biologic therapy-induced rash (see p46). These stem cell factors activate mast cells and activate substance P to act on neurokinin-1 receptors expressed by mast cells. This releases pruritogens, which induce pruritus. Using an inhibitor of the neurokinin-1 receptor will inhibit the action of substance P and so block the release of pruritogens by mast cells.

Aprepitant, commonly used to control nausea and vomiting, is an oral neurokinin-1 receptor antagonist, which blocks the mast cell degranulation mediated by NKR-1.

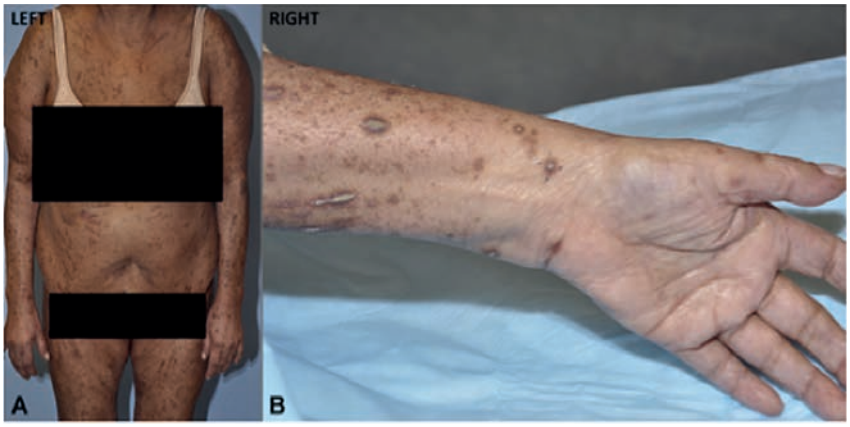
Evidence for aprepitant in the treatment of severe pruritus

The first report that aprepitant was able to reduce pruritus was published by Duval in 2009 (*NEJM* 361:1415–16). Three patients with Sézary syndrome had pruritus as the main symptom, with a severity that decreased their quality of life, scoring 7, 8 and 9 on a pruritus visual analogue scale (VAS). The pruritus could not be controlled with conventional therapy. Treatment with aprepitant at a daily dose of 80 mg was associated with a reduction in the VAS scores to 2, 3 and 2, respectively.

A publication from our group reported on two patients – a man with metastatic soft tissue sarcoma and a woman with metastatic breast carcinoma – who were receiving systemic chemotherapy. Both had pruritus that was resistant to local application of corticosteroids and to systemic treatment with antihistamines and corticosteroids. Treatment with aprepitant (standard doses: 125 mg on day 1 and 80 mg on days 2 and 3) was associated with significant improvement of pruritus in both patients 24 hours after the first administration (*Support Care Cancer* 2010, 18: 1229–30).

Two years ago we published results that demonstrated efficacy with aprepitant for the first time in erlotinib-induced pruritus. Two patients – a woman aged 44 years and a man aged 74 years – with stage IV non-small-cell lung cancer treated with erlotinib (150 mg once daily) had an acneiform rash (grade 3) resistant to steroids, with VAS scores for

PRURITUS-INDUCED EXCORIATIONS WITH THE USE OF TARGETED THERAPIES



Source: J Courtney et al. (2013) *J Am Acad Dermatol* 69:708–720

HEIKE KAMPE

pruritus of 8 and 9 (*NEJM* 2010, 363:397–398). Erlotinib was discontinued for one week and then restarted at a lower dose of 100 mg once daily, given three times over one week, on the first, third and fifth day. The patients were also given prednisone and antihistamines, but they relapsed with severe pruritus (grade 3). However, both patients showed prompt recovery from pruritus 24 hours after the first administration of aprepitant.

After two months of treatment with erlotinib with aprepitant prophylaxis, no further episodes of severe pruritus were recorded. VAS scores for pruritus were 0 and 1. This finding was very important for us, because we had not thought that the effects of the aprepitant would last as long as they did.

An overview of clinical publications reporting the use of aprepitant for the management of pruritus induced by cancer and cancer drugs shows a consistent reduction in VAS scores (see table p 47).

Prospective pilot study of aprepitant

I think that one of the most interesting publications was from our research group, published in *Lancet Oncology* in 2012 (vol 13, pp 1020–24). It was a phase II prospective pilot study in 35 cancer patients aged 18 years and over with a histologically confirmed diagnosis of a solid tumour. They had severe pruritus, with a VAS score of 7 or more during treatment with an anti-EGFR antibody or TKI. Two populations received aprepitant: the first was resistant to at least one week of systemic treatment with steroid and/or antihistamine, and the second was naïve, suffering a first occurrence of severe pruritus.

Exclusion criteria were: oral treatment with antimycotics during the four weeks preceding enrolment; topical treatment during the previous two weeks; concomitant chronic renal or hepatic insufficiency, which can both induce pruritus; and concomitant skin infection or dermatitis that would have reduced the possibility to evaluate the effect of aprepitant.

In the group of patients with steroid- and/or antihistamine-resistant pruritus with a VAS score of 7 or more, aprepitant was administered (125 mg on day 1; 80 mg on days 3 and 5) after one week of standard systemic treatment (prednisone 25 mg/day and/or fexofenadine 180 mg/day).

In the second group, the naïve patients, aprepitant was administered (125 mg on day 1, 80 mg on days 3 and 5) directly after the first onset of severe pruritus (VAS score ≥7). We measured the effect of the aprepitant using the VAS score before and after aprepitant was administered, on

INCIDENCE OF SKIN RASH WITH EGFR/TK INHIBITORS

EGFR inhibitor/TK inhibitor	Incidence of skin rash	
Cetuximab [1]	*Total 80-86%,*	*Grade 3-4: 5-18%*
Panitumumab [2]	*Total 70-100%*	*Grade 3-4: 10%*
Gefitinib [3]	*Total 53-65%*	*Grade 3-4: 2%*
Erlotinib [4]	*Total 60-79%*	*Grade 3-4: 3-10%*
Imatinib [5]	*Total 37%*	*Grade 3-4: 15 %*
Lapatinib [6]	*Total 28-45%*	-
Sunitinib [7]	*Total 19-20%*	*Grade 3-4: 1%*

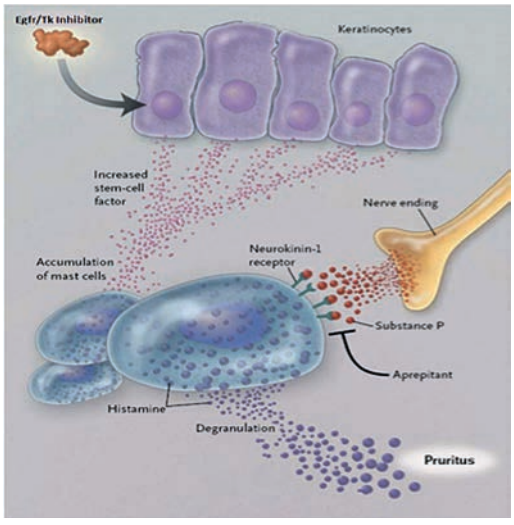
Sources: [1]R Pérez–Soler et al. (2007) *Oncology (Williston Park)* 21 (11 Suppl 5):10–6; [2]S Segaert et al. (2005) *J Dtsch Dermatol Ges* 3:599–606; [3]ME Lacouture et al. (2006) *Nat Rev Cancer* 6:803–812; [4]F Cappuzzo et al. SATURN trial. Abstract 8001 presented at ASCO 2009 Annual Meeting Orlando, US; [5]N Scheinfeld et al. (2006) *J Drugs Dermatol*; [6] http://www.ema.europa.eu; [7]RJ Motzer et al. (2007) *NEJM* 356:115–124

day 0 and day 7, and then at weekly intervals, until the biological therapy ended or pruritus recurred. The VAS score was registered in a diary given to each patient before starting the study, and noted every week throughout the study period. Response was defined as greater than a 50% reduction of pruritus intensity in comparison to the baseline value.

In terms of patient characteristics, the study included 24 patients in the refractory group and 21 patients in the naïve group. Lung cancer was the most common type of solid tumour, but 33% of the refractory group and 24% of the naïve group had colorectal cancer, and 17% and 19% of the respective groups had other types of cancer. The targeted therapy inducing pruritus was erlotinib in 46% of patients in the refractory group and in 24% of the naïve group; cetuximab was the treatment in 42% of the refractory group and 62% of the naïve group.

The results showed a statistically significant reduction in pruritus with aprepitant. The 24 patients in the group who were resistant to steroids/antihistamines had a median baseline score for pruritus intensity of 8, indicating a very high intensity of pruritus (95%CI 7.93–8.57; range 7–10; mean 8.25±0.79). After a minimum of one week of systemic therapy the median pruritus intensity decreased by a median of 23% to 7 (95%CI 6.21–7.19). However, after one week of aprepitant therapy the median pruritus intensity decreased from 7 to 1 (95%CI 0–2), representing a 93% reduction (range 0–100%; mean 81.6%), which was highly statistically significant ($P<0.0001$, Wilcoxon test). The figure opposite summarises the results in patients with pruritus resistant to standard therapy at baseline score, after one week of steroid therapy and then after one week of aprepitant.

RATIONALE FOR NKR-1 INHIBITORS IN TREATMENT OF SEVERE PRURITUS



Source: Modified from PA Gerber et al. (2011) *NEJM* 364:486–487

We saw two subpopulations of patients with refractory pruritus: the group treated with cetuximab and the group treated with erlotinib. In the cetuximab-treated population (10 patients) the median value of pruritus intensity at baseline was 8, and this decreased by 24% after standard treatment and by 93% after treatment with aprepitant, so its effect was similar to that in the study group overall. In the patients with erlotinib-induced pruritus, we saw similar results, with aprepitant reducing the pruritus VAS score to 1, with a median 85% reduction in the intensity of pruritus. Patients treated with other biological therapies – gefitinib, imatinib and sunitinib – showed similar reductions in pruritus score with aprepitant.

In the naïve group of 21 patients, the intensity of baseline pruritus was also 8 (95%CI 7.43–9.37), so it was severe. After more than one week of aprepitant the median pruritus score decreased by 100% to a median of 0 (95%CI 0.06–1.08; $P<0.0001$),

with an immediate decrease in intensity that was very similar whether the pruritus was induced by cetuximab (n=13) or erlotinib (n=5). Patients treated with other agents showed similar reductions in pruritus with aprepitant.

Another important factor to explore was the time to recurrence of pruritus: how long did the effect of aprepitant last? In our study, we found that only six patients (13%) experienced a recurrence of pruritus, with a median interval of seven weeks from the first administration of aprepitant. These patients had a further treatment cycle with aprepitant (four patients receiving cetuximab, one receiving erlotinib and one lapatinib) and showed a median decrease of 88% in pruritus. None of these patients developed any further recurrences. In our practice we have observed third and fourth recurrences of pruritus and these often, although not always, respond to further administration of aprepitant.

It is important to pay particular attention to the risk of drug–drug pharmacokinetic interactions because aprepitant can alter the activity of cytochrome P450 3A4 isoform (CYP3A4), an enzyme involved in the metabolism of a range of anticancer drugs, including tyrosine kinase inhibitors (*Lancet Oncol* 2012, 13:964–965).

Conclusions

In conclusion, pruritus is common when we use biological therapies in the treatment of cancers and, when moderate or severe, it can decrease patients' quality of life. We have demonstrated that aprepitant is effective in reducing severe pruritus induced by biological therapies in cancer patients, both in naïve and refractory pruritus. I consider that this is likely to be a class effect rather than a specific drug effect. The reduction in pruritus with aprepitant is generally long lasting – about seven weeks – in most patients, although some may have recurrences of pruritus. Aprepitant is effective in reducing pruritus irrespective of the cause, showing efficacy in patients with pruritus induced by cetuximab or erlotinib. We have not observed any toxic effect related to potential pharmacokinetic interactions between aprepitant and TKIs metabolised by the same liver cytochrome enzymes in clinical practice.

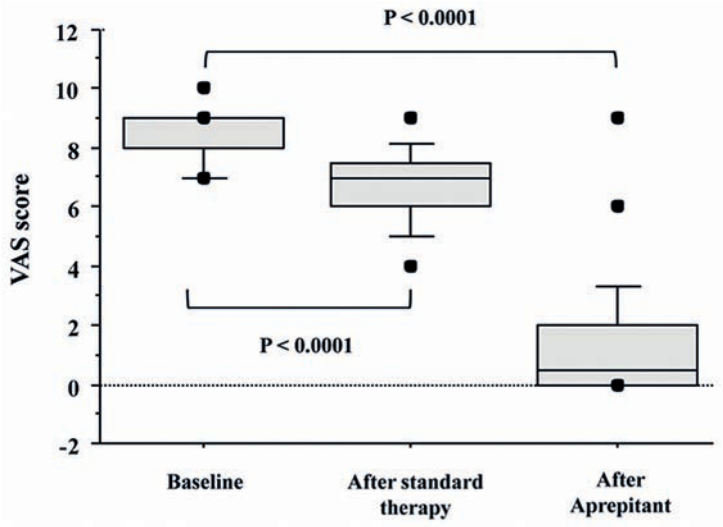
STUDIES OF APREPITANT FOR PRURITUS IN CANCER PATIENTS

Study	N	Condition	Drug	Baseline VAS	Aprepitant VAS
Santini[1]	30	Cancer	Erlotinib, cetuximab, sunitinib, imatinib, panitumumab	8.2	1.2
Ständer[2]	20	Renal, multifactorial, unknown	-	8.4	4.9
Duval[3]	3	Sézary	ECP	8	2.33
Booken[4]	5	CTCL	ECP, PUVA	9.8	4.3
Vincenzi[5]	2	Cancer	Chemo	8.5	0.5
Vincenzi[6]	2	Lung cancer	Erlotinib	8.5	0.5
Mir[7]	1	Lung cancer	Erlotinib	-	-
Total	**63**			**8.4**	**2.3**

A number of studies have reported on the use of aprepitant for managing cancer-induced and cancer-drug-induced pruritus

References [1]D Santini et al. (2012) *Lancet Oncol* 13:1020–24, [2]Ständer et al. (2010) *PLoS One* e10968; [3]A Duval et al. (2009) *NEJM* 361:1415–16; [4]N Booken et al (2011) *Br J Dermatol* 16:665–667; [5]B Vincenzi et al. (2010) *Support Care Cancer* 18:1229–30; [6]B Vincenzi et al. (2010) *NEJM* 363:397–398; [7]O Mir and R Coriat. (2012) *Lancet Oncol* 13:964–965

PRURITUS VAS SCORE AFTER STANDARD THERAPY AND APREPITANT



Source: D Santini et al. (2012) *Lancet Oncol* 13:1020–24

Fausto Roila, chair of the Medical Oncology Division at the Santa Maria Hospital, Terni, in Italy, hosted a live question and answer session

Q: *Your study, like other studies, enrolled only patients with severe pruritus and none with moderate pruritus. Do you think that moderate pruritus – pruritus that is intense, interferes with the patient's quality of life and requires oral treatment – could be treated in the same way as grade 3 pruritus or not?*

A: The problem is that it is not always easy to separate severe from moderate pruritus because it is a subjective symptom. Moderate pruritus is more frequent than severe pruritus, and there are many studies in dermatological settings showing that moderate pruritus reduces quality of life. I think that these patients should be treated with steroids, but moderate pruritus is sometimes refractory to steroids, so it would be interesting to study neurokinin inhibitors in moderate pruritus.

Q: *Only 45 patients were enrolled in your study on pruritus, so I think these results need to be confirmed in a larger trial. What do you suggest as comparator drugs for aprepitant in both patient populations – those with refractory pruritus and in those untreated?*

A: I think we need to do two different studies, one in naïve patients and the other in refractory patients. Naïve patients should be randomised to standard treatment with antihistamines and/or steroids or to aprepitant. Refractory patients should continue antihistamines and steroids and should be randomised between aprepitant and placebo. These two different studies could help us demonstrate that neurokinin inhibition is able to reduce pruritus in cancer patients treated with biological therapies.

Q: *Do you suggest preventative treatment in patients treated with EGFR inhibitors or not?*

A: I think that is another field of research. There have been no studies demonstrating the use of standard therapy in the prevention of pruritus. When we use antibodies against EGFR, for example cetuximab, panitumumab or erlotinib, moderate to severe pruritus occurs in about 20% of patients, so it could be interesting to investigate the preventive use of aprepitant in patients treated with these drugs.

Q: *In the meta-analysis and studies evaluating EGFR inhibitor-induced pruritus, the incidence of pruritus is about 22% of patients globally and severe pruritus occurs in about 2% of patients. On this basis, how is it possible to enrol patients with severe pruritus for the studies you have suggested, because we would need to screen about 2500 patients to enrol 45?*

A: The meta-analysis considered all biological therapies, so the median incidence of grade 3/4 pruritus for all biological therapies was 1.4%. In our analysis we used mostly cetuximab and erlotinib, and studies with these two drugs show the incidence of severe pruritus is about 10–15%. Also, some of the patients in our study were considered to have moderate pruritus, because we included everyone with a pruritus VAS score of 7 or more, whereas only scores of 8 or more count as severe.

Q: *In your study aprepitant was safe, with no particular adverse events reported, but you outlined the potential for drug interaction because of CYP3A4 metabolism of the EGFR inhibitors, which can be reduced by interaction with aprepitant. Perhaps the next study should include pharmacokinetic evaluation of the plasma levels of EGFR inhibitors before starting aprepitant and after its administration, to investigate and avoid the possible risk of increased toxicity.*

A: We started a new randomised phase II trial with another neurokinin inhibitor about two months ago, and we are evaluating the pharmacokinetics to check for any interaction between this neurokinin inhibitor and TKIs. This is very important for TKIs, although not for cetuximab or panitumumab, so this is an important issue to study. However, in our practice we did not observe any increase in toxicity related to TKIs, perhaps because the dose of aprepitant was very low because we used a median of three administrations of aprepitant every month.

Q: *Do you think that antihistamines and a course of steroids are effective in controlling radiotherapy-induced pruritus for skin irritation and skin toxicity?*

A: I think that topical treatments are the most effective treatments to reduce pruritus induced by radiotherapy. However, it depends if you use radiotherapy with biological therapies, because there are some studies showing that the skin toxicity induced by radiotherapy can be increased by the activity of biological therapies and it could be a synergistic effect. ■

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Redefining the primary objective of phase I oncology trials

MARK RATAIN

Cytotoxic agents are conventionally dosed on the basis of the maximum tolerated dose defined in phase I trials. A study assessing adverse events in over 2,000 patients treated with molecularly targeted agents suggests a need to redefine criteria for dosing of molecularly targeted agents, which should be based on randomised, dose-ranging phase II trials.

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Cytotoxic chemotherapy has been the mainstay of anticancer treatment for decades. However, in the past 20 years, we have witnessed the successful development of many noncytotoxic drugs, often referred to as molecularly targeted agents (MTAs), a targeting approach used in multiple therapeutic areas. Whereas the dogma of chemotherapy has always been to administer all drugs at the maximum tolerated dose (MTD), it has been recognised that such dogma would not be expected to apply to MTAs. The oncology field has been unique in its focus on MTD; other therapeutic areas do not use such an approach. In this context, the European Organisation for Research and Treatment of Cancer (EORTC) contacted 16 academic institutions and pharmaceutical companies for the purpose of reviewing adverse events from 2,084 patients enrolled in 54 phase I trials.1 On the basis of this review, the authors concluded that there is a need to redefine the criteria used for defining the recommended phase II dose, to consider not only traditional acute grade 3–4 toxic effects, but also chronic grade 1–2 adverse events.

Although the EORTC analysis is sound and its conclusions logical, the authors have not acknowledged the challenge of distinguishing drug-related adverse events from disease-related adverse events in patients with advanced-stage cancer. In particular, fatigue and liver function test abnormalities are common clinical events in this population with or without treatment. Surprisingly, the EORTC report does not acknowledge that dose-dependent chronic toxic effects are not unique to MTAs, but are common to many widely used chemotherapeutic agents (for example, neuropathy due to vinca alkaloids, taxanes and platinum compounds; cardiac toxicity due to anthracyclines and anthracenediones; and nephropathy due to cisplatin).

The most important question is whether or not it is critical to precisely define a 'recommended phase II dose' as part of a phase I trial. I would argue that it is finally time to model our drug development paradigms on those routinely used in other chronic diseases, rather than trying to remodel our ancient oncology paradigms to fit modern oncology drugs. As noted in the 1994 International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)–E4 Guideline, "dose-response should be an integral component of drug development".[2] The Guideline also notes that the highest tolerated dose will not always be optimal, and suggests a number of different phase II designs to capture this information: parallel dose-response, crossover dose-response, forced titration, and optional titration (placebo-controlled titration to endpoint). In this context, the EORTC analysis is less relevant, as the question of optimal dose can only be addressed in randomised dose-ranging phase II

trials, with analysis of both efficacy and toxicity endpoints.

Randomised dose-ranging phase II trials have infrequently been used in oncology. One example was a randomised phase II study of temsirolimus in kidney cancer, which concluded that weekly doses of 25 mg, 75 mg, and 250 mg were equivalent, leading to the selection of 25 mg for phase III trials.[3] However, the use of randomised dose-ranging designs in oncology is not new, as noted by its use in the development of anastrozole 20 years ago, which established that daily doses of 1 mg and 10 mg were equivalent,[4] and these doses led to the selection of 1 mg for phase III trials.

With the advent of the FDA Breakthrough designation, there have been recent attempts to use focused phase I trials as a basis for accelerated drug approval. A recent example is the development of ceritinib for patients with ALK-rearranged lung cancer, which received accelerated approval by the US FDA on 29 April 2014 on the basis of such a trial.[5] Although there is indisputable activity of ceritinib at the approved dose of 750 mg, there is also significant uncertainty regarding the optimal dose and prandial conditions for administration.[6] Despite the poor solubility of ceritinib under physiological conditions, it was administered under fasting conditions in the phase I trial, and was subsequently demonstrated to have a clinically significant positive food effect, with its area under the concentration time curve (AUC) increased by 58% when given with a low-fat meal and 73% when given with a high-fat meal.[7] Furthermore, as dose reduction for severe or persistent gastrointestinal toxicity occurred in 38% of patients, the FDA hypothesised that this toxicity might be alleviated by administering ceritinib at a lower dose (450–600 mg) when given with food, thereby maintaining therapeutic concentrations while reducing gastrointestinal drug concentrations.[8] In this context, a randomised study testing this hypothesis has been mandated by the FDA as a post-marketing requirement, and if the FDA hypothesis is confirmed, would presumably result in re-labelling of the drug at the lower dose. However, such a label change could be problematic to Novartis, as it would require an increase in the price per mg of the drug to avoid a 25–40% reduction in sales.

> **"It is finally time to model our drug development paradigms on those routinely used in other chronic diseases"**

Given the desire to rapidly advance promising drugs, what should we expect to conclude about dosing as a result of a phase I study? We certainly should understand the qualitative toxic effects of a drug, and aim to gain some understanding of the relationship of dose and AUC in relation to acute toxic effects. Depending on the population studied, there may be little understanding of the chronic toxic effects of the drug (and even less understanding of those that are dose-dependent). Thus, the EORTC recommendations regarding defining optimal dosing are not really assessable in a phase I trial, and are best addressed in a subsequent randomised dose-ranging phase II trial.

Of great concern is the relatively modest attention paid to pharmacokinetic issues in some phase I studies of MTAs. Using the ceritinib study as an example,5 the published article reporting the phase I trial includes only one paragraph on pharmacokinetics, with additional data included in the supplementary appendix. The issues raised by the FDA in its review regarding prandial conditions were not addressed in this article, which does not even mention that this oral kinase inhibitor was administered under fasting conditions, a circumstance often resulting in decreased bioavailability.[9]

One cannot make any decisions regarding phase II dosing without a full understanding of the pharmacokinetics of a drug, on the basis of one or more carefully conducted phase I studies. These include the relationship of dose to AUC, the magnitude of both inter-individual and intra-individual pharmacokinetic variability, and the impact of prandial conditions on exposure. More attention needs to be paid to these fundamental pharmacokinetic issues, and less attention to tumour biopsies, expensive imaging studies, and detailed measurements of tumour lesions.

Furthermore, phase II trials should include two or more doses, as routinely done with MTAs in other therapeutic areas (such as rheumatoid arthritis).[10] Consequently, phase I oncology trials should focus on defining a range of phase II doses rather than a single phase II dose, determining both an upper limit (maximally tolerated dose) and lower limit (minimally effective dose), which may be hypothetical and based on plasma concentrations and/or serum biomarkers. Randomised phase II trials should evaluate dose-response and dose-toxicity, as recommended by the ICH. Only then can the optimal dose be determined. ■

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References for this article can be found at www.cancerworld.org

newsround

Selected reports edited by Janet Fricker

Decisional aids increase patient knowledge and reduce regret

British Journal of Cancer

Use of decision aids can potentially increase knowledge and reduce decisional regret around clinical trial participation, a recent study has found. But the joint Australian and UK study, representing the first randomised controlled trial of a decision aid, found they have no effect on reducing decisional conflicts experienced by patients.

While research has demonstrated support for clinical trials as a way to improve oncology care, patients commonly fail to understand the rationale and design of clinical trials, which could potentially compromise informed consent. Decision aids have been developed to optimise informed consent by helping patients weigh up pros and cons. They supplement verbal guidance from clinicians by presenting clear written and graphical information about options and outcomes.

In the study, Ilona Juraskova and colleagues, from the University of Sydney, Australia, and Queen Mary College, London, investigated whether decision aids reduce decisional difficulties among women considering participation in the International Breast Cancer Intervention Study-II (IBIS-II) trial. IBIS-II was an international multicentre study evaluating anastrozole versus standard treatment in two groups of post-menopausal women – those at elevated risk of breast cancer without breast symptoms (IBIS-II Prevention) and those recently treated for ductal carcinoma in situ (IBIS-II DCIS).

For the current trial, participants were randomised to receive a trial pack with additional decision aid information (n=141, of whom 109 were in the prevention group and 32 in the DCIS group), or to a control group who just received the trial pack (n=149, of whom 114 were in the prevention group and 35 in the DCIS group).

The primary outcome was 'decisional conflict score', assessed using the validated decisional conflict scale containing 16 items designed to measure the amount of uncertainty patients have regarding a course of action, and factors contributing to that uncertainty.

Results for the prevention cohort show that the decisional conflict score was 15.7 for the decision aid group versus 13.2 for the control group (P=0.4); while for the DCIS cohort the decisional conflict score was 20.7 for the decision aid group versus 11.9 for the control group (P=0.1).

For the prevention cohort, the secondary outcome score of decisional regret, measured after three months, achieved a score of 10.1 in the decision aid group versus 16.0 in the control group (P=0.04). Also in the prevention cohort, decisional satisfaction after three months was 4.62 in the decision aid group versus 4.42 in the control group (P=0.07).

In the DCIS cohort, no significant differences between decision aid and control groups were found for decisional regret and decisional satisfaction. However, in this cohort, the decision aid group had an objective knowledge score of 77.6 compared to 63.8 for the control group (P=0.008).

"The results suggest that decision aids may improve the informed consent process by increasing knowledge and reducing decisional regret. However, different results were found in the Prevention and DCIS cohorts, suggesting that trial population characteristics are important in determining intervention efficacy," write the authors.

I Juraskova, P Butow, C Bonner et al. Improving decision making about clinical trial participation – a randomised controlled trial of a decision aid for women considering participation in the IBIS-II breast cancer prevention trial. *BJC* 1 July 2014, 111:1–7

Frail breast cancer patients less likely to receive hormone therapy

Journal of Clinical Oncology

Frailty is associated with hormone therapy not being initiated in older breast cancer patients, but does not predict early discontinuation, finds a prospective cohort study.

Women over 65 years make up nearly half of breast cancer patients and are predicted to account for increasing numbers due to ageing populations. While older breast cancer patients are eligible for adjuvant hormonal therapy, its use is not universal. For the study, Vanessa Sheppard from Georgetown University, Washington, and colleagues, examined

the influence of frailty on hormonal therapy non-initiation and discontinuation. The concept is used to capture functional status, and although prior studies have considered age, comorbidity, or functional status, none have included the 'multidimensional construct' of frailty, which encompasses daily functioning, and physiologic, cognitive, and emotional reserves. For the study, functional status and levels of comorbidity were considered as distinct entities from chronological age.

Between January 2004 and April 2011, a prospective cohort of 1,288 women with a mean age of 72.8 years diagnosed with invasive non-metastatic breast cancer was recruited from 78 centres and asked to undertake baseline interviews. Frailty was measured by adapting a 35-item scale (developed by Searle et al) to predict mortality in older people living in the community. This included self-reported items relating to limitations in activities of daily living, sensory deficits, and pre-diagnosis co-morbidity. Hormonal initiation was defined from records and discontinuation from self-report.

Results (analysed for the 1,062 patients with ER-positive tumours) showed that 76.4% (*n*=803) had scores in the robust range (0 to <0.2); 18.7% (*n*=197) in the pre-frail range (0.2 to <0.35); and 4.9% (*n*=51) in the frail range (>0.35). Overall only 14% of subjects failed to have hormone therapy initiated; and among those who had hormone therapy initiated, 79.3% (*n*=710) received an aromatase inhibitor, and 21.7% (*n*=185) tamoxifen or another selective ER modulator.

In univariable analyses, several factors were found to relate to non-initiation of treatment, including age (OR=1.04; 95%CI 1.01–1.07 per 1-year increase; *P*=0.007); non-white race (vs white; OR=1.69; 95%CI 1.04–2.75; *P*=0.034); and frailty or pre-frailty versus robustness (OR=1.77; 95%CI 1.21–2.58; *P*=0.003). Continuation of treatment at five years was 41% for those in the frail group versus 50% in the robust group (*P*=0.045).

"This study demonstrates that the overwhelming majority of older women initiated adjuvant hormonal therapy, but nearly half discontinued treatment before 5 years... Even after considering chronologic age, women who were frail or pre frail tended to have higher odds of noninitiation," write the authors.

The relationship between higher frailty and non-initiation, they add, could indicate that women and/or their providers have considered the balance of life expectancy and the probability of recurrence within remaining life expectancy. "An alternative explanation is that women with greater frailty may have been concerned about adverse effects based on interactions of hormonal therapy and specific co-morbidities, such as cardio- and/or cerebrovascular disease, and risk of thromboembolic events," they add.

■ V Sheppard, L Faul, G Luta et al. Frailty and Adherence to Adjuvant Hormonal Therapy in Older women with Breast Cancer: CALGB Protocol 369901. *JCO* 22 August 2014, 22:2318–27

Training needed to recognise low health literacy

■ Patient Education and Counseling

Low subjective health literacy among women with ovarian tumours was associated with less perceived information provision about medical tests and lower information satisfaction, a Dutch study has shown. Healthcare providers require training to identify patients with low health literacy, suggest the authors.

Adequate information has been shown to be an unmet need among cancer survivors through all phases of their disease. Effective provision of information is recognised to require an individualised approach tailored to patients' needs, competences, limitations and possible barriers to use of health information.

In the current study Nicole Ezendam and colleagues, from the Comprehensive Cancer Centre, The Netherlands, investigated associations between health literacy and perceived levels of information provision and information satisfaction, controlling for education. Prior to the study, the authors hypothesised that lower health literacy and education levels would both be associated with less perceived information provision and satisfaction.

For the study, 548 women diagnosed with ovarian cancer or borderline ovarian tumours between 2000 and 2010, registered in the Eindhoven Cancer Registry, were invited to fill in questionnaires that addressed educational levels, employment status and marital status, and also asked about their perceived levels of, and satisfaction with, the information provided. Additionally, a Dutch adaptation of Chew's three-item Set of Brief Screening Questions (SBSQ) was used to evaluate subjective health literacy, asking patients to rate how confident they felt filling out medical forms on their own ("very", "quite", "somewhat", "a little" or "not at all").

Of the 275 women who responded (50%), 13% had low health literacy, 41% medium health literacy and 46% high health literacy. Additionally, 55 (20%) had high educational levels, 171 (62%) medium educational levels, 40 (15%) low educational levels and 9 (3%) unknown educational levels.

Hierarchical multiple logistic regressions revealed no significant associations between educational levels and information satisfaction, but in comparison to patients with high subjective health literacy, women with low health literacy were significantly less likely to be satisfied with information received (OR=0.2, 95%CI 0.1–0.6).

"In the present study, lower subjective HL [health literacy] was associated with less perceived information provision about medical tests and lower information satisfaction," write the authors, adding that contrary to their initial hypothesis, low educational levels were associated with more perceived information provision about disease compared to high levels. But health literacy and educational levels, they add, explain a relatively small amount of variability in perceived information provision and information satisfaction.

Low educational levels, they point out, do not necessarily imply low learning capacity, and other patient characteristics, such as coping styles, also have a part to play.

"Findings from our study highlight the need for low HL to be identified and managed within cancer care. As health care providers may overestimate their patients' HL they might need specific training about recognizing low HL in patients and strategies that can be used to enhance their communication with patients with low HL," write the authors.

■ M Verkissen, N Ezendam, M Fransen et al. The role of health literacy in perceived information provision and satisfaction among women with ovarian tumors: A study from the population-based PROFILES registry. *Patient Educ Couns* June 2014, 95:421–428

Classification system shows prognostic and predictive value in lung adenocarcinoma

■ Journal of Clinical Oncology

In patients with lung adenocarcinoma receiving adjuvant chemotherapy, the IASLC/ATS/ERS classification system delivered significant prognostic and predictive information for death and recurrence, a Taiwanese study has concluded. The investigators showed the information could be used to stratify patients for aggressive adjuvant chemoradiotherapy.

In the study, Wen-Hu Hsu and colleagues, from Taipei Veterans General Hospital, in Taiwan, set out to explore the relationship between histologic subtyping according to the new International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS) classification system and recurrence.

The classification system recommended using comprehensive histologic subtyping to semi-quantitatively assess histologic patterns in 5% increments to define the single predominant pattern (lepidic, acinar, papillary, micropapillary, or solid) for invasive adenocarcinomas.

Between January 2004 and December 2010, 573 patients who underwent complete resection for lung adenocarcinomas at Taipei Veterans General Hospital were retrospectively reviewed.

Results show that, among the 573 patients, 35 (6.1%) were found to have lepidic-predominant tumours, 193 (33.7%) acinar-predominant tumours, 155 (27.1%) papillary-predominant tumours, 112 (19.5%) micropapillary-predominant tumours, and 78 (13.6%) solid-predominant adenocarcinomas.

At a median follow-up of 47 months, 58.5% of patients (n=335) were free of tumour recurrence, 32.5% (n=186) had developed recurrence and 9% (n=52) had unknown recurrence status.

Recurrence was significantly higher in patients with micropapillary- and solid-predominant adenocarcinomas than among those with other types of tumours (P<0.01).

Micropapillary- and solid-predominant adenocarcinomas also had a significantly higher possibility of developing initial extrathoracic-only recurrence than other types (P<0.01)

The pattern of initial recurrence of the five predominant histologic patterns was not significantly different according to local/distant (P=0.36) or intrathoracic/extrathoracic recurrence (P=0.25), and no significant differences for pleural effusions were found among the five predominant histologic patterns (P=0.23).

Patients with micropapillary- and solid-predominant adenocarcinomas had a significantly higher probability of having initial extrathoracic-only recurrence than those with lepidic-, acinar-, or papillary-predominant adenocarcinomas (P<0.01).

Patients with micropapillary-predominant tumours showed decreases in overall survival compared with patients with other tumours predominating (HR=1.4, 95%CI 1.0–2.1, P=0.06), as did patients with solid-predominant tumours (HR=2.3, 95%CI 1.6–3.5, P<0.01).

"In conclusion, the IASLC/ATS/ERS classification system has significant prognostic and predictive value for survival and recurrence, which will likely affect clinical decision making in the near future. This information is important for designing clinical randomized trials for aggressive adjuvant therapy," write the authors.

■ J Hung, Y Yeh, W Jeng et al. Predictive value of the International Association for the Study of Lung Cancer/ American Thoracic Society/European Respiratory Society classification of lung adenocarcinoma in tumor recurrence and patient survival. *JCO* 1 August 2014, 36:2357–68

Patient support delivers timely cancer care

■ JNCI

Providing systematic support to patients with abnormal cancer screening results or cancer moderately improved achievement of "timely" cancer care, the Patient Navigation Research Program (PNRP) has found.

Patient navigation – support and guidance offered to people with abnormal cancer screening results or cancer – was devised to address health disparities among people from ethnic minorities and lower income groups. Although rapidly becoming a standard of care, previous studies have reported mixed findings for patient navigation, with some reporting the achievement of more timely care and others not.

In the current study, Karen Freund, from Tufts University School of Medicine, and colleagues, undertook the first multicentre clinical trial (involving nine centres) to examine benefits of patient navigation in participants with breast, cervical, colorectal or prostate screening abnormalities and/or cancer between 2007 and 2010.

Navigation was initiated after a clinician informed the participant of the abnormal test

result, with programmes including opportunities for face-to-face interaction between participants and navigators as well as telephone and mail contact. Navigators also worked with families, healthcare providers, and social service agencies to identify resources to address barriers to care.

Altogether 10,521 participants with abnormal cancer screening results were enrolled, of whom 5,063 received the 'navigation' intervention and 5,458 acted as the controls who did not. Furthermore, for the 2,105 patients with a diagnosis of cancer or of precancerous lesions, 1,032 received the navigation intervention and 1,073 acted as controls who did not. The first outcome of interest was whether and when diagnostic resolution of the abnormal cancer screening result was achieved, and the second was time to initiation of treatment for participants with invasive cancer or precancerous lesions.

Results show that there was no benefit for those receiving 'navigation' during the first 90 days of care, but that benefits for patients in the navigation group in comparison with the control group were seen from 91 to 365 days, for both diagnostic resolution (HR=1.51, 95%CI 1.23–1.84; $P<0.001$) and treatment initiation (HR=1.43, 95%CI 1.10–1.86; $P<0.007$).

"In conclusion, the PNRP demonstrates the effectiveness of patient navigation in settings where resources are low or there is a history of poor follow-up rates and among patients at risk of failure to comply with follow-up or treatment recommendations after an abnormal cancer screening test," write the authors.

The finding of no benefit in the first 90 days, they add, may reflect the time required to connect navigators with participants. The finding that 13% of participants with abnormal breast cancer screening results were not able to be contacted by their navigator within 60 days, they add, supports this view.

The impact of patient navigation was greatest among centres with low baseline resolution or treatment initiation rates in the control arm. "This speaks to a need for patient navigation services in settings that possibly have few resources to assist underserved participants to complete timely diagnostic resolution and initiate cancer treatment," the authors conclude.

■ K Freund, Tracy Battaglia, E Calhoun et al. Impact of patient navigation on timely cancer care: The Patient Navigation Research Program. *JNCI* June 2014, 106(6):dju115

MR-guided ultrasound helps bone pain

■ JNCI

MR-guided focused ultrasound surgery (MRgFUS) offers a safe and effective, non-invasive treatment for alleviating pain from bone metastases in patients who have failed standard treatments, a US trial has found. The study represents the first completed phase III study of MRgFUS in oncology.

Bone metastases are common among patients with advanced cancer, and pain due to bone metastases is a frequent cause of cancer-related morbidity. Radiation therapy, together with systemic therapies and analgesics, is the standard of care for localised metastatic bone pain, although up to two-thirds of patients have residual pain after radiotherapy, leaving limited treatment options.

MRgFUS is a non-invasive technique combining focused ultrasound (FUS) with magnetic resonance (MR), enabling physicians to perform precise localised tumour tissue ablation. FUS delivers acoustic energy to heat lesions focally to ablative temperatures of more than 65°C.

Between July 2008 and May 2012, Mark Hurwitz from the Bodine Center, Philadelphia, and international colleagues, randomly assigned 147 patients 3:1 to MRgFUS ($n=112$) or placebo ($n=35$). The placebo treatment for the study, which took place in 17 centres across the US, Canada, Israel, Italy and Russia, was identical to MRgFUS, but with sonication power switched off. While patients with up to five painful lesions were eligible, the single treated lesion had to cause at least two points' greater pain on the Numerical Rating Scale (NRS) than any other lesion.

The primary endpoint was a composite of change from baseline in worst NRS scores (0–10 scale) and morphine equivalent daily dose (MEDD), with patients considered responders if their worst NRS had decreased by at least two points and their MEDD had not increased by more than 25% from baseline to three months.

Results show that the primary endpoint was achieved in 64.3% in the MRgFUS arm versus 20.0% in the placebo arm ($P<0.001$). At three months the change from baseline in worst NRS was 3.6 for the MRgFUS group versus 0.7 for the placebo group ($P<0.001$), and there was also a statistically significant improvement in the Brief Pain Inventory (a measure of functional interference of pain on quality of life) for the MRgFUS group ($P<0.001$).

The most common treatment-related adverse event was sonication pain, which occurred in 32.1% of MRgFUS patients. Furthermore, two patients had pathological fractures, one patient had third-degree skin burns, and one patient suffered from neuropathy. Overall, 60.3% adverse events resolved on the day of treatment.

"MRgFUS provides durable pain relief and improved function in patients who failed radiation or those who are not candidates for or declined radiation. Given the impact of these clinically significant results, coupled with a favorable side-effect profile, MRgFUS should be considered a viable treatment option for painful bone metastases," write the authors. Further studies, they add, are required to assess the role of MRgFUS in patients with bone metastases as first-line therapy.

■ M Hurwitz, P Ghanouni, S Kanaev et al. Magnetic Resonance-Guided Focused Ultrasound for Patients with Painful Bone Metastases. Phase III Trial Results. *JNCI,* June 2014, 106(5):dju082

The heroic role of the caregiver in oncology

Doctors in Tel Aviv teamed up with a photojournalist to learn more about the role of the 'unsung heroes' who place their patient–companion at the heart of their world.

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Our Tel Aviv Medical Center, a municipal hospital, is the primary provider of oncologic services to Jewish and Arab residents of both Tel Aviv and Jaffa. Today's oncology departments host not only patients but also the caregivers who help their patients navigate diagnostic, therapeutic, and ancillary services within the modern cancer care centre. Because caregivers frequently serve as liaisons between patients and healthcare teams,[1] everyone involved benefits when team members understand the caregiving role and value the caregiver's presence.[2]

What is caregiving?

In the setting of cancer medicine, the "caregiver" is typically an unpaid individual, outside the frame of professional health care workers,[3] who is dedicated to maintaining the well-being of another person, the patient. In the caregiver–patient relationship, the role of caregiver requires attending selflessly to diverse issues associated with malignant disease. Caregivers may provide support on many levels, from emotional and spiritual to cognitive, medical, economic, and legal.

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The caregiver's involvement is dynamic and redefines itself throughout the different phases of the patient's illness. For example, in early phases, the need to assist in the processing of information is paramount; whereas, in latter phases, concerns typically turn to assessing uncertainty about the future, altered social relationships, and financial issues.[1]

In a supportive role, the caregiver is typically less visible than the patient-protagonist around whom most cancer centres revolve. Caregivers usually develop unique bonds as "companions" to the patients whom they accompany. Prager stated that caregivers rarely receive recognition, and have therefore become the "unsung heroes" of the medical system.[4]

Prager also lists several determinants that might motivate caregivers, such as love, sense of duty, and even feelings of guilt.[4] Even when individuals become caregivers reluctantly,[5] the process of caregiving ultimately results in sacrifice, devotion, and commitment. Regardless of the factors that prompt action, caregivers are most often deeply devoted to assisting their patient–companions.

Challenges of caregiving

As more studies focus on the stresses associated with caregiving,[6,7] it is becoming apparent that caregivers not only sacrifice their time and independence but also sometimes their health. A recent report by Rohleder et al. draws attention to the physiologic costs of caring for patients with cancer.[6] The report characterises the changes in caregiver neurohormonal profiles (e.g. diurnal output of salivary amylase) and anti-inflammatory signaling (e.g. linear decline in mRNA). Compared with age-appropriate non-caregivers, caregivers are prone to psychological distress, economic hardship as a function of time lost from work, and diminution of health-related quality of life.[8]

In a comprehensive review, Northouse et al. proposed an array of caregiving research questions involving assessment of caregiver preparation, further documentation of caregiver physical and psychological health, and examination of interfaces between caregivers and technologies such as smartphones.[9] The review suggests the construction of a base of evidence to further the understanding of caregiving and its ramifications.

Photodocumentary study

With a goal of contributing to that evidentiary base, we obtained approval from our institutional review board to carry out a photodocumentary study of caregivers within our oncology department setting. Our staff nurses identified patients, with their caregivers, who might be willing to participate in the study. We secured permission not only to take

A caregiver feeds his wife hot soup on a cold winter's day. Then, he engages her in conversation

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A mother is present for her son. Solemnity prevails

photographs but also to display the photos for public viewing in gallery exhibitions.

An experienced photojournalist captured spontaneous, unposed pictures. To create captions, staff physicians, nurses, psychologists, social workers, and receptionists participated in group discussion. Recognising that the pictures were likely to evoke intense emotional responses, we reassured all captioning-process participants that there were no "correct" responses. The final captions reflect not only reactions to the photo images but also recollections of the original interactions between caregivers and patients. Shown here are samples of the resulting photographs, illustrating several themes characteristic of caregiving.

Each of the exhibit's caregiver pictures may convey, as the familiar saying goes, "a thousand words" about the special people who, by placing their patient–companions in the centre of their world, commit to doing battle against cancer. We hope that our photos will help to inspire each member of the healthcare team to recognise the importance of the "unsung hero" caregivers who accompany their patients, will encourage caregivers' support of patients, and will encourage the healthcare team to invite caregivers to participate, as appropriate, in the healthcare decision-making process.

References for this article can be found at www.cancerworld.org

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