European School of Oncology
Learning to care

July-August 2013

Number 55

cancerworld

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Cancer World is published six times per year by the European School of Oncology. It is distributed at major conferences, mailed to subscribers and to European opinion leaders, and is available online at www.cancerworld.org

The right place for the right patient... at the right cost

NICOLA NICOLAI GUEST EDITOR

Debates about the benefits and drawbacks of centralising the planning and delivery of cancer services in a few large referral centres, such as featured in the March–April issue of *Cancer World*, are important in teasing out key challenges in balancing high quality with accessibility in cancer care. However, it is the economics of austerity that will determine how this debate evolves.

Cancer survival varies not just between but also within countries. Poorer survival rates cannot simply be blamed on lack of referral centres, because the quality of referral centres varies according to the technical and scientific resources available. Centres should be funded according to how effectively they perform, taking into account measures such as length of hospitalisation, rates of complications, disease recurrence and re-admission.

Economic analysis should include costs of examinations and treatments, but also the cost of obliging patients to travel a long way (to both the patient and the economy in lost output), and the risk that barriers to travel may mean some people will not access facilities that could benefit them.

Effective community-based healthcare services are needed for early diagnosis, prevention and screening. Rather than concentrating all cancer care in a few large referral centres, it may be better to differentiate healthcare facilities according to the intensity of care, concentrating major medical and surgical procedures, with a high risk of complications, at a few hospitals with exceptional levels of expertise.

Minimum criteria are needed to ensure all cancer units and centres provide high-quality services in staging and treating cancer. These may include a critical mass of patients, a core team, a non-core team, non-medical healthcare professionals, systematic data collection, multidisciplinary management of patients, and educational activity. Patient advocates should be involved to promote education and empowerment of patients, focusing on their needs for logistical help and social support

Guidelines are very helpful in promoting knowledge, though they don't always improve efficiency. IT systems are essential to support effective communication and allow clinicians to share information quickly. Out-sourcing certain facilities and treatments can work, but will be counterproductive without shared guidelines and patient pathways. Centres of expertise must be able to keep up their technical know-how of core clinical activities, as this is where practitioners develop their professional competencies and gain clinical experience.

The big challenge is first knowing how to get all these elements – effective preventive intervention and early detection, high standards of care, cost-effectiveness and better communication – to work together, and then building the political will to drive through the changes.

Modern organisational models can help create well-structured networks: national or regional interdisciplinary working groups that link primary care, hospitals, referral centres, health administrators, GPs and patient advocates. Key elements must include regular multidisciplinary meetings, shared guidelines, and agreements between centres for access to facilities that are not available locally.

Nicola Nicolai is a urology surgeon working with the Prostate Cancer Programme, Istituto Nazionale dei Tumori, Milan, Italy

Semir Beslija: the sky's the limit in Sarajevo

SIMON CROMPTON

Semir Beslija's tenacious efforts have built the Sarajevo Oncology Institute from 'zero' at the end of the war, to the regional centre of excellence and trusted trials centre it is today. Choosing the right people, he says, has been key to his remarkable achievement.

The taxi driver who is weaving through the Sarajevo rush-hour traffic speaks good English. He wants to know why an Englishman like me wants to go to the Clinical Centre of Sarajevo University – the city's main hospital on a hill on the edges of the city. I tell him I'm going to interview Semir Beslija, head of the medical oncology department. He's an important man, I tell him.

"Yes, I know," he says. "You're not going to take him away to London are you?"

It's a familiar story to my taxi driver. The high flyers, many newly qualified doctors, all look outside Bosnia Herzegovina to higher salaries in Austria, Italy or beyond. He too wants to escape Sarajevo, a city not just struggling with the legacy of a horrible war, but now in the grip of economic recession. He likes the look of Barcelona: "It's too dark here," he says.

But there's no danger that Semir Beslija will leave. The Institute of Oncology at the Clinical Centre is, along with his family, what gives his life meaning. He worked at the Clinical Centre as a junior doctor throughout the siege of Sarajevo between 1992 and 1995, providing care without electricity, heat and running water, as shells burst around the damaged building. And during that time, he pledged to himself that he would help rebuild the institute and bring to it a state-of-the-art clinical oncology department.

Now, 20 years later, he has. Watching Beslija march confidently down the cool corridors of the well-equipped centre, greeted by everyone he meets, shaking hands, offering advice, he has the aura of a proud business owner. Before the war the Clinical Centre could treat just a few hundred cancer patients a year with radiotherapy and surgery alone. Today it has a comprehensive cancer centre – the only one in Bosnia Herzegovina – with a multidisciplinary

approach to cancer diagnosis and care, a new breast unit, and a proud record of undergraduate and postgraduate teaching.

When Beslija started the medical oncology department in 1998, he was the only doctor, with two beds. Now he has 11 doctors and 62 beds, housed in brand new buildings opened two years ago. He shows me the outpatients department, bedecked in brilliant tangerine and blue, capable of accommodating around 100 chemotherapy patients a day; an MRI scanning suite, with three brand new machines; upstairs, a newly opened unit for participants in phase I clinical trials – the first in the region.

This is not just another regional success story. Semir Beslija, now 47, has put Sarajevo on the international cancer map. Three months ago, he tells me, a delegation of leading doctors from Gothenburg in Sweden visited the Sarajevo Clinical Centre to see if there was any assistance they could offer. The director of the Centre sent them to spend the afternoon in Beslija's clinical oncology department. Later, the Swedish professor reported back to the director and joked: "There must be some sort of misunderstanding. We aren't able to help that young man in charge of clinical oncology: we need help from him."

"I am very proud," he tells me. "We are not witnesses in the revolution in oncology. We are the actors here in Sarajevo."

Perhaps most importantly, Sarajevo is a valued participant in international trials. "In the Department of Medical Oncology, we are currently running 16 global randomised controlled trials. In HER2-driven breast cancer, we have six molecules under investigation in my institution – probably one of the few centres in Europe to be doing this. You know what it means to have it in Sarajevo? You wouldn't believe. Because we started from zero."

VELIJA HASANBEGOVIC

The cancer success story in Sarajevo is all the more remarkable because of its grim background. Beslija, like most inhabitants, wants Sarajevo to be characterised by the present, not the past. The war has become like a millstone round the city's neck, defining it and dragging it back. But he also acknowledges that it is etched into the consciousness of every citizen.

Even to the casual tourist, it is omnipresent in the bullet holes that pockmark the city brickwork, and the gleaming graveyards that astound you in parks, on street corners, and down the hillsides. Over the three and a half year siege of Sarajevo, the city was cut off from the world, with no power, food or water. Around 12,000 residents were killed in the fighting and bombardment.

"Only those who were here can understand what happened in the war," he says. "I could talk to you about the war for a year, but I am not sure you would come one micron closer to understanding it."

Though Beslija would like the story to begin after the war, in truth it began in 1991 when he decided that he wanted to become the first ever medical oncologist in Bosnia. Born and bred in Sarajevo, his father an agricultural engineer, he had decided at the age of seven that he would be a doctor – "I always knew". Having graduated in medicine at its medical school in 1988, Beslija specialised in internal medicine at the Clinical Centre of Sarajevo University. He initially wanted to head into gynaecology – inspired by his uncle who followed the same profession. But jobs were hard to find, so he began to investigate opportunities in the oncology department.

Everyone thought he was mad: one of the most promising young doctors in the country looking for a job in the clinic with the lowest profile in the Sarajevo Clinical Centre? The cancer clinics had just five doctors, and their most sophisticated piece of equipment was a cobalt radiotherapy machine. Most Sarajevo cancer patients travelled to Belgrade (in modern Serbia), Zagreb (in modern Croatia) and Ljubljana (in modern Slovenia). But Beslija was enthused by the exciting new specialty of medical oncology, and wanted to change things.

Then the war started. Beslija joined the Bosnian army as a medical officer. As bullets and bombs rained down on Sarajevo, he started to live a strange divided life. By day, he was trying to get his education in internal medicine and do his best for patients with cancer. By night he was out in the field, tending to wounded and dying soldiers.

"It was not an easy job," he says, avoiding the details. "It was unbelievably hard turning from people who were actually dying there and then, to people with cancer. Because it was two totally different kinds of approaches. It was very hard to think about oncology during the war. We didn't have drugs, we didn't have electricity for radiotherapy, so perhaps the greatest part of our activity for cancer patients was..." He is lost for the word. "...Empathy."

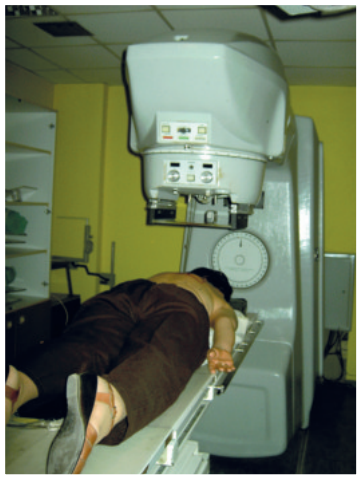
"But working in the Clinical Centre was important to us, because it was some sort of connection with the previous life. It kept alive the hope that some day oncology will once more become important."

"Every day I was dreaming that eventually I would go abroad, finish my education and start the medical oncology department here. The war was hugely motivating. Those four years are probably the period of my life I am most proud of."

I ask him why. He replies simply: "Because I stayed."

The war has become like a millstone round the city's neck, defining it and dragging it back

LT. STACEY WYZKOWSKI



Then and now. Beslija stayed through the four-year siege to do what he could with two beds, one ancient cobalt machine and intermittent electricity; today he has 11 handpicked doctors, 62 beds, 1 in 5 patients in trials and he runs the first phase I unit in the region

Beslija met his wife Narcisa in the dermatology department of the Clinical Centre during the siege. She was another young doctor, later to become a psychiatrist, and Beslija remembers how astounded he was by her long black hair: "because we had no water, I couldn't believe how she kept it looking so beautiful." They married on a glorious April day in 1995: "It was a beautiful war wedding, with the grenades coming down. We were worried about the safety of our guests, but everything was fine."

"After the experiences my wife and I had during the war, everything else in life becomes one million times easier. If you can find the best solution for you and your family in war, after that the sky's the limit. And because of that, war is an important part of all people here. War changes everything because you just have one priority, to stay alive, and you learn that everything else is... nothing."

On his office wall, there are pictures of Beslija shortly after the war ended. He is a thin, gaunt young man with a beard, unrecognisable from the buoyant and muscular doctor squeezed into a white coat who sits at the desk in front of me.

VELIJA HASANBEGOVIC

The fact is that within months of the siege starting, half of the Clinical Centre staff left Sarajevo – fleeing with their families while they could. A skeleton staff, including Beslija and Hiba Basic, then head of the hospital's Department of Radiation Oncology, did what little they could for the cancer patients, and deep bonds developed between them all. Basic (see *Cancer World* Nov–Dec 2010) died late last year, and Beslija admits to missing her terribly.

After the war ended in 1995, the couple moved to Slovenia so that, with the help of an ESMO scholarship, he could continue his training at the Institute of Oncology in Ljubljana (his wife gave up a well-paid job with an American non-governmental organisation so that he could do so). In the course of his placement there, he also became a visiting doctor in Milan, at the European Institute of Oncology, and spent three months at the MD Anderson Cancer Center in Houston, Texas, as a guest scholar.

He returned to the Clinical Centre of Sarajevo University in 1998 and took the position of medical oncologist. Then he set about the task of creating a working department, organising the unit for out-patient chemotherapy, forging links with other institutions internationally, finding investment for new equipment, and creating a modern teaching space for students and residents.

VELIJA HASANBEGOVIC

Over 15 years, his most important priority has always been to surround himself with the right people. In creating a new service from scratch, choosing the right personnel has been far more important than equipment, drugs or advanced technology, he says.

"This is a lesson from the war," says Beslija, whose work as Associate Professor at Sarajevo Medical School has helped him find the right people. "My main rule has always been that I choose doctors personally: I count on their behaviour, their humanism and the qualities they bring from home. When you have young people like this, it is very easy to make them into excellent medical oncologists." Interestingly, most of the doctors he appoints are themselves children of doctors.

All of Beslija's medical oncologists are from Sarajevo, and all have stayed with him since their appointment – a rather different picture from the gloomy one painted by the taxi driver. What keeps them working in their home country despite higher pay elsewhere, he says, are the excellent working relations and honesty in the department. Plus the fact that all doctors have excellent opportunities for exchange and continuing education in oncology centres in Europe and the United States – the result of Beslija's networking efforts. "In medicine, you always have to give people some sort of challenge, to fulfil their expectations," he says.

But despite Beslija's emphasis on the importance of his staff, you can't get away from the fact that his department is founded on his persistence, intelligence and force of personality. At first sight he looks serious, intimidating even, but he has a power to engage with his passion and his honesty about his achievements. His words persistently reveal glimpses of a conviction about the underlying value of soul, empathy and humanity – perhaps most of all about the value of human life.

This has stood him in good stead in his national and international engagements to try and gain funding and make Bosnia part of the

international cancer community. In 2010 he covered 300,000 miles as he attended meetings around the world. He has to be a good politician, he acknowledges, as well as a good manager and a good doctor.

Over the past ten years, Beslija and his counterpart in the radiation oncology department, Nermina Obralic, have built the reputation of cancer services at the Clinical Centre, and as a result have attracted funding from local and national government, the World Bank and European funding agencies. This has allowed investment in new buildings, beds and equipment. Around 90% of the buildings and infrastructure of the Institute of Oncology is less than five years old.

They have linked with organisations such as the European School of Oncology, which supported the education of many doctors and nurses at the centre, and helped it set up international conferences in Sarajevo such as the international Interconference Breast Cancer Meeting, held every two years. Beslija joined societies such as ASCO and ESMO (he is currently national representative for Bosnia Herzegovina).

Perhaps most importantly, Beslija managed to overcome negative perceptions about the abilities and facilities of oncologists in the region so that they could become involved in international trials. This meant that the department had new sources of income; that patients had access to new treatments which otherwise would be too expensive; and that doctors were less liable to burn out because they were not faced with the frustration of not having the right treatments available.

This only became possible because, 15 years ago, Christoph Zielinski, director of the Division of Oncology at the University of Vienna, Austria, took at leap of faith. Beslija made a point of meeting him at a cancer conference in Europe, to tell him about his vision for Sarajevo. Zielinski asked him to be involved in a trial of a medicine for metastatic breast cancer. It involved 90 women and Beslija conducted it by himself, every day after his clinic finished at 4pm. He was working a 20-hour day for one and a half years.

"The trial was later published in the *Journal of Clinical Oncology*. Can you imagine my pride, six years after the end of the war, the name of my institution in the best oncology journal? It was amazing. Now people knew about Sarajevo because of oncology, not because of the war, or the First World War, or the Winter Olympics. I will be grateful to Professor Zielinski all my life. After that, everything became easier, because the door was open."

The centre has now become a regional centre of excellence for clinical oncology trials and is in a position to refuse around 35% of trial offers. Two of the young doctors in Beslija's team already have 10 years' experience as principal investigators. Today, around a fifth of patients are involved in trials – most of them in Beslija's main interest areas of breast and gastro-intestinal cancers. "That is unbelievable, because I still believe strongly that the best possible way to treat a patient is participation in a good randomised controlled trial."

"To be part of the global story like this is 100 times harder for Sarajevo than Munich, or Milan. You have to be 100 times better to meet expectations from sponsors. We have been."

Sarajevo's breakthrough is now being reflected elsewhere in the region. Beslija is on the scientific board of the Central European Cooperative Oncology Group, formed in 1999 to bring together centres of clinical oncology from central and southeastern Europe so that they can design and conduct clinical trials to the highest standards. Professor Zielinski is President.

"I think these regional collaborative groups are showing the Western world that there's great activity and great potential in the region," says Beslija. "Through publishing articles, through announcements at European conferences, at ASCO and so on."

Beslija points to the increasing international profile of oncologists such as Tanja Čufer (from Slovenia – see also *Cancer World* May–June

"Can you imagine my pride, six years after the end of the war, the name of my institution in the best oncology journal?"

"It gives me a little push, and makes me all the more determined to show how good the people here are"

2007), Eduard Vrdoljak (Croatia) and Alexandru Eniu (Romania) as indications that the cancer community in Eastern Europe is becoming less marginalised. "If you have excellent people, who are part of important oncological associations, and who are breaking borders, things that look impossible can be done. We are witnessing that strongly in this region, and I have to say that I have a lot of patients who were on treatment in Paris and Munich, and come back here, and the treatment is just as good."

But the picture is not all rosy. Ask Beslija about the biggest challenge that he and his Eastern European colleagues in oncology face, and the answer is still prejudice. "The first association that many oncologists in the Western world have about Sarajevo is the war – the bad," he says.

He tells me that his grandfather was a priest in the Bosnian part of the Austro-Hungarian Empire army (Bosnia Herzegovina was occupied and then annexed by the Austro-Hungarian Empire between 1878 and 1918). He could travel without restriction to Vienna without any problems, as could every Sarajevo inhabitant 100 years ago. Yet after the war in the 1990s, the European Union imposed visa restrictions on Bosnian travellers, which clearly angers Beslija, who feels that he and professional colleagues are stigmatised by having to stand in queues at airports for hours when lecturing in other countries.

"I remember that when we held our Breast Cancer Conference here in 2005, we had oncologists from Western Europe who didn't want to come. They didn't feel safe. And still sometimes, when you say you come from Sarajevo, they look sorry for you."

"But it also gives me a little push, and makes me all the more determined to show how good the people here are. It is becoming better. You cannot find something of any significance in oncology now without names from this part of Europe, which was not the case ten years ago. Hopefully, at the end of the day, quality will be recognised."

Beslija insists his main motivation is not proving a point about his country: it is giving the best possible oncology care to his people. "They deserve it," he says. With five chemotherapy and radiotherapy centres elsewhere in the country, and a clinical oncology department now established in Banja Luka, the ripples of quality are spreading nationally.

Still working 16 hours a day, Beslija insists he enjoys every minute of life. Somewhere he finds the time to cook at home, to enjoy wine, to ski – most importantly of all, to spend time with his family. He clearly dotes on his daughter Majda – born when he was in Ljubljana nearly 17 years ago – who has a passion for horses, he says, which exceeds his own for oncology. She wants to go into equine medicine.

But he is contemplating a change. This year he has been officially appointed director of the Institute of Oncology and, with a remit for radiotherapy, surgery and pathology as well as clinical oncology, he plans to spend the next two years improving coordination between the centre's 43 clinics and engaging national and international support so that the centre can develop even further.

"I will have to be even more of a politician now," he says.

But when he is 50, he adds, he will slow down, and commit himself wholly to clinical investigation. No one has infinite supplies of energy. As Beslija finishes his guided tour of the Institute, he gives an indication of the emotional as well as the physical investment he has made as we pause at an upstairs window with a panoramic view of Sarajevo. It looks glorious in the Spring sunshine, nestled beneath the wooded mountains from which it was once bombarded.

"I am so proud," he says, reflecting on the thriving facilities we have just seen. "It is like building your own home, brick by brick." Then he points out a tower block below, still scarred by a massive star-shaped hole from a shell which hit it two decades ago. "You see that?" he says. "These are reminders." Then he taps his head. "But they are always in here too." ■

Exploiting a nano-sized breach in cancer's defences

MARC BEISHON

It's long been the stuff of science fiction, but could the prospect of nanotechnology systems that deliver 'atomic bombs' direct to cancer cells soon become reality?

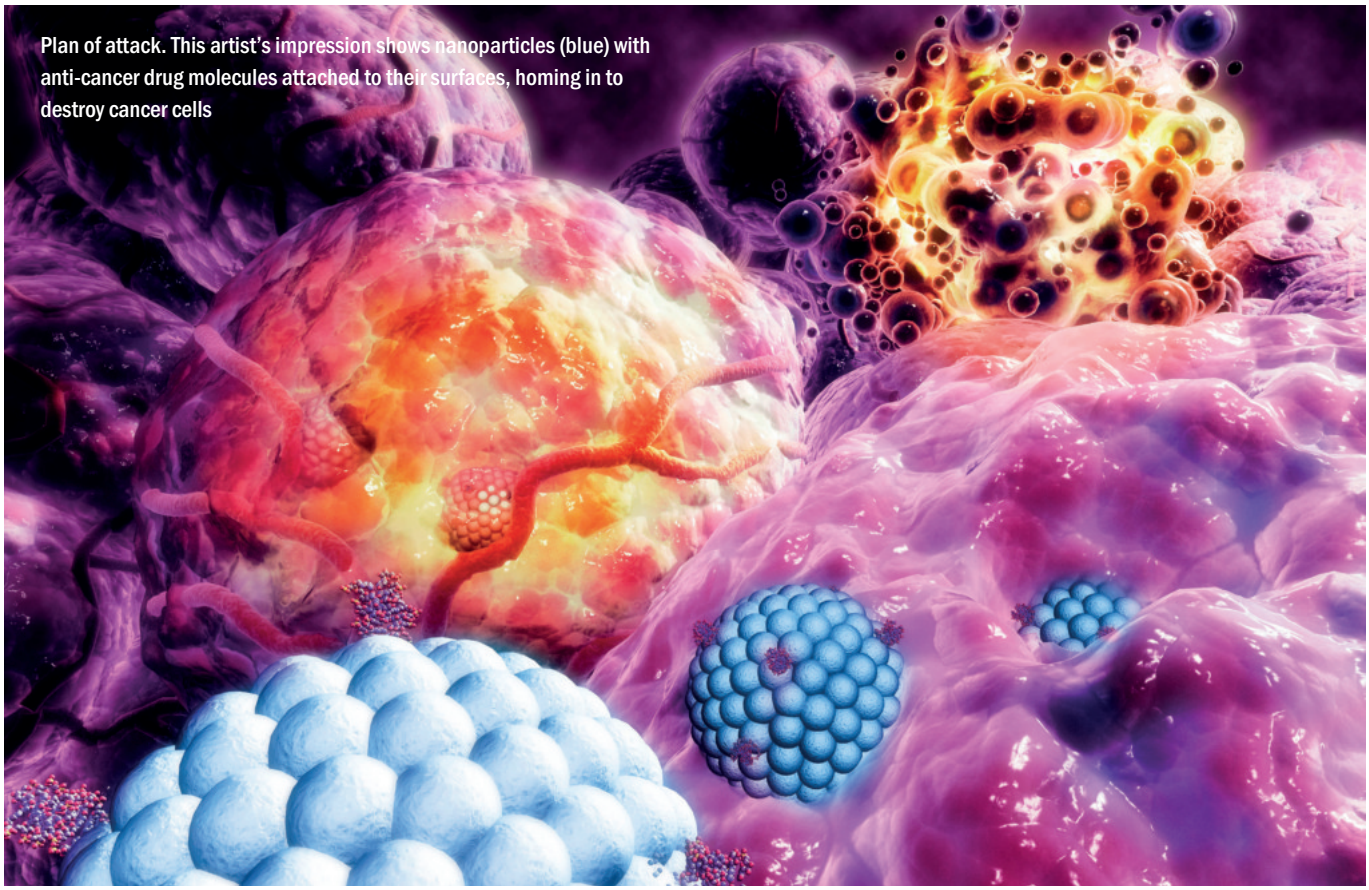
It's a compelling vision: tiny particles, primed with a highly effective cancer killing drug, able to move round the body and seek out and destroy tumour cells, only releasing their deadly payload when they reach their target. That's precisely what many research teams are now developing with nanotechnology, a rapidly growing field concerned with the properties of materials at the nanometre scale – particles of 10^{-9} metres, a size that is bigger than molecules but smaller than human cells (if a nanoparticle were a football, a red blood cell would be the size of a football field).

If indeed nanoparticles can find their targets they could open up a new era of cancer treatment that avoids several big obstacles with usual drug therapy. By holding toxic chemotherapies inside shells made from substances such as polymers, the rest of the body can be protected from harmful side-effects, and drugs can circulate for longer, with more finding the target. Drugs that have been too toxic to use before are now making a reappearance in nano form, and to help them find the target, nanoparticles are also being designed with specific tumour-seeking agents, in a further development of the field of targeted biological therapy.

Combining primary targeting (getting to where tumours are, and even chasing down circulating cancer cells) with secondary targeting (attacking cancer cells and structures inside the cell) is what is making nanotechnology potentially so exciting.

And that's only part of the story. Other therapies in development don't involve chemotherapy at all. Some, for example deliver pieces of genetic materials to turn off genes implicated in cancer cell growth; others concentrate metallic particles that can kill tumours when external radiation such as heat is applied. Nanoparticles can also be injected directly into tumours, or even by inhaler, for delivering lung cancer therapies direct to the tumours.

There is also a rapidly growing interest in the use of nanotechnology in diagnostics (see page 17). It is the therapeutic use of nanotechnology that has captured the most headlines, however, especially as the main applications in development are for treating advanced disease in



Plan of attack. This artist's impression shows nanoparticles (blue) with anti-cancer drug molecules attached to their surfaces, homing in to destroy cancer cells

MEDI-MATION/SCIENCE PHOTO LIBRARY

patients for whom other approaches have had little success.

EXPLOITING AN ACHILLES HEEL

Key to the potential of nanomedicine in cancer is a crucial difference between healthy and cancerous cells that these techniques can exploit. While cancer is notorious for its ability to evade treatment, at the nanoscale – at least on a mechanical basis – solid tumours have a fundamental weakness, as Jennifer Grossman, a scientist at the Nanotechnology Characterization Laboratory in the US, part of the National Cancer Institute (NCI), explains. "We have known for some time that particulate matter can accumulate in inflammatory sites such as tumours. Inflamed tissues have a different vasculature than healthy tissue because the blood vessels grow very quickly and irregularly and have pores or holes that are big enough for a nanoparticle to pass inside – but the particles are too big to get through the wall of a healthy blood vessel. So when you inject them into the bloodstream they stay there except through these pores in tumour vasculature."

That is simplified description. The scientific term for this is the enhanced permeability and retention (EPR) effect, where retention refers to the lack of lymphatics in tumours, which helps to stop particles draining away quickly. It has only been verified in animal models, she says, and while all human tumours have 'leaky' vasculature, this varies greatly depending on the cancer type. The effect also depends on tumour size, and small tumours may lack enough vasculature to be targeted.

At the nanoscale – at least on a mechanical basis – solid tumours have a fundamental weakness

Too small, and they can be filtered out in the kidneys, too large, and they may not penetrate the tumour

The difference in size of the openings between healthy and tumour tissue can be huge – just 2–4 nanometres for healthy tissue and several hundred nanometres for cancer blood vessels. With the US putting its weight behind nanotechnology (the 21st century Nanotechnology Research and Development Act came in 2003), researchers – and in particular chemical engineers and material scientists – have since helped to determine the optimum size and other properties for nanoparticles, such that they have a good chance of reaching tumours.

Too small, and like small molecule drugs they can be filtered out in the kidneys unless bound to blood proteins; too large, and they may stay in blood vessels and not penetrate a tumour, and they also need to evade the body's defence system, which carries foreign bodies such as viruses to the spleen and liver (although the latter is itself a common site for metastases and a target itself).

As Mark Davis, a chemical engineer at Caltech (California Institute of Technology) has reported, it turns out that the limits for particles are 10–100 nm, with 30–70 nm being about optimum. Davis became a pioneer in cancer nanoparticles after his wife was diagnosed with the disease. With others he has gone on to determine more design features that are important, as well as experimenting with a huge array of possible materials and structures that could optimise delivery of drugs and other agents such as gene silencing with fragments of RNA. Because nanoparticles have the special property of a large surface area relative to volume, researchers have put much emphasis on coatings that can both pave the way to the tumour and engage with it.

OVERCOMING BARRIERS

Grossman details a range of factors that stand in the way of particles even getting to a tumour, despite the attraction of the EPR effect. First, there is the body's phagocyte system, which protects against viruses and other foreign bodies. The chances of being carried away by this can be reduced by applying a coating such as polyethylene glycol (PEG), which she says also adjusts the electrical charge of the particle surface to make it less likely to be attracted to healthy cells before it reaches a tumour.

Then the tumour itself has its own protective shell – the stroma – which is made up of a number of structures including a collagen matrix, which Grossman notes can be very dense in some tumours such as pancreatic, and which can stand in the way of drugs (and is one reason for the poor outlook for these cancers). Tumours can also have a high fluid pressure because they lack drainage, which can impede the inflow of particles. And if nano-drugs only reach the edges of tumours and have limited effect, then drug resistance could build up. It's no wonder that new fields such as 'transport oncophysics' are springing up to help find ways around the barriers.

Apart from the design of particles (such as disguising them as red blood cells, which some groups are doing) there are many approaches to aiding their passage, such as using antiangiogenic drugs to lower pressures in tumours.

With several functions to perform, it can be hard to build these particles with the necessary quality and purity in sufficient quantities for large-scale use. Adding more complexity can also adversely affect desirable properties such as the ability to circulate long enough in the bloodstream, though the opposite can also pose a problem: nano-drugs combining a carrying device as well as drugs can be difficult to eliminate from the body.

Questions remain about whether cancer nanotechology has too many such barriers to move ahead. Development of new therapeutics and diagnostics is still mostly in the hands of academic and government research labs and start-up biotech companies, particularly in high-tech 'clusters' such as around Boston in the US. However, large pharmaceutical companies have recently struck deals with some of the start-ups, indicating a step change in investment and potential, and a number of new nano-drugs have reached phase II and III stages.

This is a field that is also bringing together different disciplines, which cancer visionaries feel will be crucial, in one way or another, to making advances – physicists, engineers, material scientists, computing experts and chemists are among those making the running in cancer nanotechnology, alongside colleagues

in biology and the clinic. The combined brain power now focusing on cancer nanotechnology is formidable, while other branches of nanomedicine are also emerging.

IN THE CLINIC

The first nano-drugs use the passive targeting of the EPR effect to accumulate in tumours and diffuse their payload; much of the new generation are taking an active approach by using targeted coatings such as antibodies, proteins and peptides that bind to tumour cells and only then release a drug that diffuses in the tumour, or enters tumour cells.

For drug delivery to tumours, the first application – Doxil, or Caelyx in Europe – was approved as long ago as 1995 by the US FDA and is approved for recurrent ovarian cancer, relapsed multiple myeloma, metastatic breast cancer and Kaposi's sarcoma. Now out of patent, today's biotechnology experts consider it to be very much a first-generation nanoparticle, as it is not on the same small scale or 'smartness' as systems now being engineered, and relies only on passive targeting.

Doxil is made from a liposome, which comprises a fatty sphere surrounding a core that contains doxorubicin – a chemotherapy with dose-limiting toxicity. It also has a polymer coating that allows it to stay in the bloodstream longer (but can cause skin side-effects). A similar nano-drug, Myocet, does not have the coating, and is approved in Europe and Canada for treating patients with metastatic breast cancer. The benefit of both these nano-drugs when used in breast cancer lies in their reduced heart toxicity, as there is no reported gain in efficacy. This nano-approach set in train the search for ways to deliver therapies that would be too toxic to be approved for more systemic administration – both new and existing drugs that may have been abandoned or denied approval on safety grounds in the past.

Another nano-drug in use is Abraxane, which was approved more recently in the US (2005) for metastatic breast cancer, and raised hopes that it would finally usher in a lot more agents. It is formulated to overcome a different type of toxicity, and has also been found to be more effective than the conventional drug at second line or more – in this case paclitaxel (Taxol), which is insoluble and so is prepared with a solvent that can cause side effects. Abraxane attaches paclitaxel to nanoparticles made from the human protein, albumin. A Japanese company, NanoCarrier, currently has a phase III trial of paclitaxel using nanoparticles made instead of polymeric micelles, which are also able to carry insoluble drugs.

There are a few other approved nano-drugs – a recent one that gained

THE GROWING FIELD OF NANO-DIAGNOSTICS

Nanoparticles are also being researched and deployed in a number of cancer diagnosis, imaging and biomarker applications. These include:

- Increasing the contrast and detection ability of CT, MRI and PET imaging with various targeted nanoparticles made with materials such as gold, silica and iron oxide.
- Screening blood samples with nanowire chip devices primed with antibodies to detect tiny numbers of circulating cancer cells.
- Investigating nano-structures such as cantilevers to detect genetic mutations in cancer cell RNA.
- Swedish researchers have also reported on how nanoparticles can be used in 'theranostics' – imaging tumours using nanoparticles and also using them for drug therapy. Adding imaging to nanoparticles is likely to be a key tool in nano-drug development.
- Quantum dots – tiny crystals that glow – are being looked at for applications such as image-guided surgery, although there are toxicity concerns.
- Meanwhile, researchers at MIT have found a way of amplifying weak biomarkers – peptides coated on nanoparticles can be released into the bloodstream by certain proteases that are often produced by cancer cells and then detected in urine.
- Using a sensor made of densely packed carbon nanotubes coated with gold nanoparticles, a team at the University of Connecticut has developed a device capable of detecting oral cancer from samples.

Much of the new generation are taking an active approach by using targeted coatings that bind to tumour cells

"We have great technology from top academic centres, but you have to have something that is usable in trials"

accelerated approval from the FDA is Marqibo, a liposomal formulation of the cancer drug vincristine, for patients with relapsed acute lymphoblastic leukaemia that is negative for the Philadelphia chromosome.

IN THE PIPELINE

While other potential nano-drugs have investigational approval, the momentum depends on pushing the boundaries from the first-generation products and gaining investment from mainstream drug development. As Elisabet de los Pinos, chief executive of Aura Biosciences, one of the biotech firms in the Boston cluster, says, nanotechnology involves a change of mindset – not drug discovery but better drug delivery for the large number of drugs already known to be effective. "While we have some phenomenal new targeted agents such as monoclonal antibodies, they are often given in combination with very toxic drugs such as the platinums, which are still used in every lung cancer patient. We need to deliver a targeted 'atomic bomb' directly to the tumour."

Viral delivery

The technology that Aura Biosciences is using is based on viruses, which could better deliver treatments by combining small size and more precise targeting. "We are piggybacking on nature with viruses, because they are below 100 nanometres and already penetrate the body's barriers," says de los Pinos. "But you also need to better distinguish between normal and tumour cells, so you need a targeting method – and technologies based on materials such as polymers and carbon structures have a problem when you want to deliver a toxic agent. You need to be specific in where it's delivered, otherwise you won't get approval to use it."

The virus particles that Aura is building are called pseudovirions, which are synthetic viruses but without any viral DNA – they are simply protein shells – and a group at the NCI has found they possess a critical property of 'infecting' tumour cells but not normal ones. De los Pinos, a Spaniard whose background is molecular biology, says making use of this natural propensity to target tumour cells is the unique approach her company is taking, and that she was set on virus technology from the start of her venture, looking at various approaches being developed in Europe and the US, opting eventually for technologies from France and the US, and also then establishing the company in the Boston hotspot.

"Like most biotech firms we have great technology from top academic centres, but you have to scale it so we have something that is usable in clinical trials, which is what we have been working on for the last year or so. It's not straightforward because the technology is novel and we are the only ones doing it, but we are ready now to get the approval from the FDA to dose a first patient."

De los Pinos won't disclose the treatment that could go into a first human trial with Aura's pseudovirions, but animal models have demonstrated uptake in metastatic ovarian cancer and non-small-cell lung cancer. Aura has some heavyweight backing, including José Baselga, the Spanish medical oncologist and former ESMO president, who is now chief physician at the Memorial Sloan-Kettering Cancer Center in New York, and is a member of the company's board of directors.

Ligand loaded polymers

On Aura's doorstep in Boston are other companies focused on new ways to deliver anti-cancer therapies, and some have moved into clinical trials – with varying success so far. Bind Therapeutics, which was co-founded by Robert Langer, a biotech pioneer and chemical engineer at MIT, has polymer-based particles it calls Accurins, which achieve targeting with ligand molecules attached to the particle surface. So far, the company has completed a phase I study for its BIND-014 agent, which is an Accurin containing docetaxel and which targets the prostate-specific membrane antigen (PSMA), a cell-surface protein that the company says is abundantly expressed on certain cancer cells and on new blood vessels that feed a wide array of solid tumours.

Bind's technology has certainly impressed several large drug companies: Amgen, AstraZeneca and Pfizer have signed up to deals worth several hundred million dollars in total for nano-delivery of agents that are yet to be specified, but will include targeted drugs such as kinase inhibitors.

Greater toxicity more safely

Meanwhile Cerulean Pharma, with which Caltech's Mark Davis is involved, had progressed to a phase II trial for its lead candidate, CRLX101, which carries camptothecin – a highly potent anti-cancer agent that was discovered in the 1960s but only used in less potent derivatives, namely irinotecan and topotecan. Cerulean's technology uses cyclodextrins, made up of sugar molecules, linked to a polymer, to create nanoparticles with a slow-release mechanism to target tumour cells. However, the phase II study, conducted in more than 150 patients with advanced lung cancer in Russia and the Ukraine, did not show survival benefit – a setback for the company, though it does have other ongoing trials and technology.

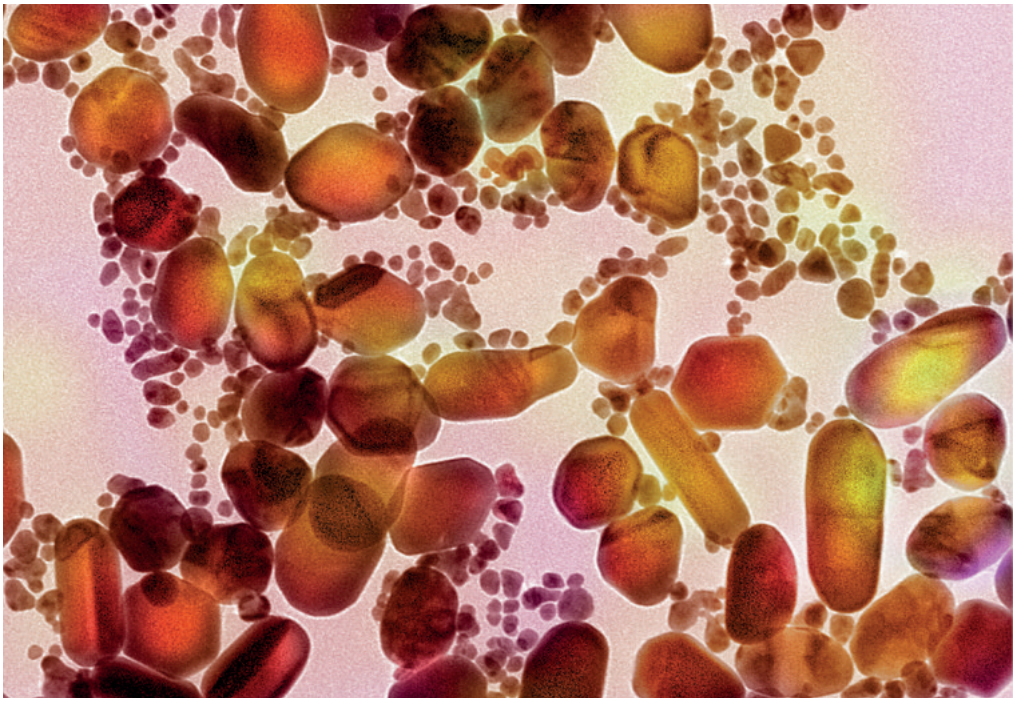
A liposome nano-drug containing irinotecan has reached phase III – Merrimack Pharmaceuticals is running the NAPOLI-1 study for second-line metastatic pancreatic cancer patients. The particle relies on the natural blood flow of the tumour to direct the therapy to the cancer.

The many possibilities of metals

Metals are another class of material that are being used for therapeutic applications, although Grossman says that, as they do not degrade, there are concerns about safety if they persist in the body. But metal particles are a major avenue for researchers and biotech firms. CytImmune Sciences, for example, another firm in the Boston area, has completed a phase I trial of gold nanoparticles carrying tumour necrosis factor (TNF), a toxic agent that targets tumour vasculature. Gold has properties that make it especially useful at the nano-level, but other metals are being used.

Ian Baker, a materials scientist and director of the Dartmouth Center for Cancer Nanotechnology Excellence in the US, says that among his projects are investigations of iron nanoparticles that, once located in tumours, can be heated to destroy cells – in this case by using a technique called magnetic hyperthermia, where a magnetic field heats iron oxide particles. "The idea of hyperthermia has been around for long time, but the problem is that tumour cells don't respond differently to heat than normal cells, so we need to inject the particles locally or tag them with antibodies so they find their way to the tumour. Mostly what we are doing is heating, but one project is looking at heating to release a drug. We can cure cancer in mice with hyperthermia, and are looking to do clinical trials, but there are more restrictions in the US."

A team in Germany, he notes, has been working on magnetic hyperthermia for more than 20 years; a company called MagForce has so far taken the technology to a phase II trial in grade IV brain tumours (glioblastoma multiforme) and a phase I in pancreatic and prostate tumours. Apart from destroying the cells by heating, or thermal ablation, the particles are also said to sensitise tumours to chemo- or radiotherapy. Clearly there could be important crossovers here with other disciplines such as interventional radiology and radiation



DAVID MCCARTHY/SCIENCE PHOTO LIBRARY

Gold nanoparticles. A phase I trial has recently been completed using tiny gold particles to carry TNF (tumour necrosis factor) to cancer cells; other metals are also being tested using a variety of techniques

There are a number of trials at phase I/II aimed at silencing various protein expressions

oncology: another example is French firm Nanobiotix, whose NanoXray particles enhance radiotherapy.

Gene silencing

Potentially one of the most elegant uses for therapeutic nanoparticles is to carry segments of RNA that can directly turn off genes in cancer cells, and so bypass the expressed proteins that are the usual targets of drugs – if they can be targeted at all. A number of research groups are involved with siRNA – small interfering RNA molecules – which are delivered by nanoparticles, as RNA does not survive for long on its own after injection into the bloodstream. There are a number of trials at phase I/II aimed at silencing various protein expressions, such as from the aptly named British firm, Silence Therapeutics, Alnylam Pharmaceuticals and Arrowhead Research in the US, the latter a majority owner of a firm that Mark Davis founded and which was the first to demonstrate that a targeted nanoparticle could deliver siRNA in a human cancer patient.

It's even possible to assemble these RNA molecules into a nano-structure built from DNA, which researchers at MIT in the US have done, showing that the resulting particles survive long enough in animal models to reach tumours.

DNA origami

Björn Högberg, a principal investigator at the Swedish Medical Nanoscience Centre at the Karolinska Institute, Sweden, is also researching DNA. "We don't care about the genetics but see DNA as a building material for nanoparticles in different shapes – circles, rods, crosses, smiley faces – anything we want. It's called DNA origami and is like 3D printing technology for nanoscale objects, and we can design one in just a few days and get a high yield of particles."

In published work, Högberg and his team have designed a DNA nanoparticle that carries the chemotherapy drug doxorubicin, which "likes to attach to DNA", he says "We can attach molecules like this and know exactly where they will sit. Other nanoparticle technologies don't have this perfect positional control." This is early work, he adds, but the way it would work is that doxorubicin would better diffuse to a tumour cell's DNA and block cell reproduction.

MACMILLAN PUBLISHERS

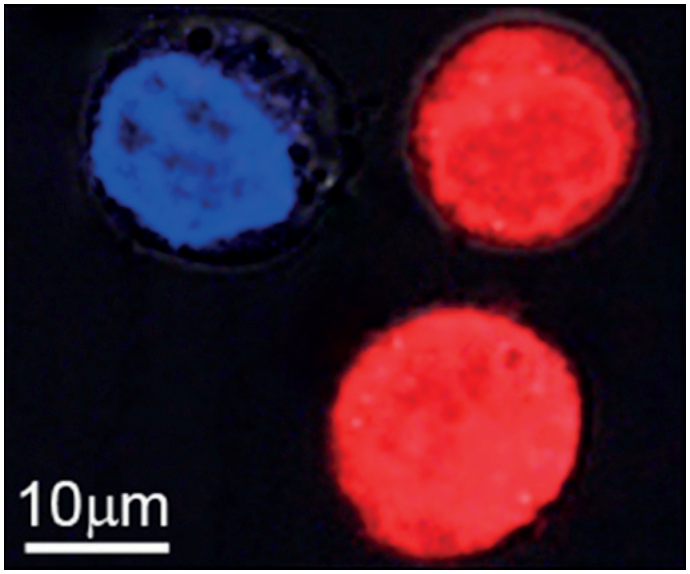
An A–Z of DNA. The extraordinary versatility of DNA as a material for building nano-particles makes it ideal as a carrier of multiple molecules, such as a drug and a targeting agent.

Reprinted with permission from Macmillan Publishers Ltd: *Nature*, Complex shapes self-assembled from single-stranded DNA tiles, 2012

A NANO-BOOST FOR EUROPE?

The US probably has a lead in cancer nanotechnology, thanks to the NCI Alliance for Nanotechnology, which funds 'centres of excellence' such as Baker's Dartmouth Center for Cancer Nanotechnology Excellence, and also product partnerships and training centres, although Baker says the funding does not extend to clinical trials.

Grossman's facility – the Characterization Lab – provides a free service for biotech companies to test the properties of nano-formulations, including animal testing, for safety and efficacy, and is a collaboration between



PLASMONIC NANOBUBBLE LAB/RICE UNIVERSITY

Plasmonic nanobubbles. In this therapy, which is being developed at Rice University, Houston, Texas, bubbles form around heated gold nanoparticles that target cancer cells. When the particles are hollow, bubbles form that are large enough to kill the cell when they burst; when they are solid, the bubbles are smaller and can punch a temporary hole in a cell wall, allowing drugs or other material to flow in

the NCI, FDA and the US National Institute of Standards and Technology. This service is a particular strength, she says, because of the complexity of nanoproducts. "There's a natural heterogeneity for nanoparticles, as they are made of thousands of atoms, so we need to characterise their purity and quality – it's more complicated than making a small molecule drug." More than 300 different nano-formulations developed by over 75 research groups have been 'characterised' so far, and at least six are in clinical trials.

Grossman says officials at the European Commission are interested in setting up a similar characterisation capability in Europe, and to that end she's recently had a meeting in Brussels to highlight the work of the NCI lab, which could be good news for the growing number of biotech firms on this side of the Atlantic. An announcement about work around establishing an EU nanotechnology characterisation facility, and collaboration with the US, was expected from the European Technology Platform on Nanomedicine (ETPN) – a high-level group of industry and academic scientists – at the European Summit on Clinical Nanomedicine in Basel in late June.

Last February saw the launch of the European School of DNA Nanotechnology, an Initial Training Network under the EU's 7th framework programme, which is set to run for four years. A joint initiative by leading scientists from academic centres in Denmark, Germany, Sweden (Karolinska Institute, where Högberg is based) and the UK, which also involves commercial companies, the School aims to train early-stage researchers specifically in the interdisciplinary field of DNA nanotechnology, and to promote the foundation of new bionanotechnology start-up companies.

The question is whether all this will be enough to persuade pioneers like Elisabet de los Pinos, that Europe can offer the supportive environment needed for success. ■

WORK IN PROGRESS

Nanotechnology offers an enormously wide range of potential therapeutic approaches. Among those being actively explored are:

- A drug-containing DNA box that opens only after it encounters certain protein keys from cancer cells (such as leukaemia cells)
- Inhalable nanostructured lipid nanocarriers that find cancer cells in the lung, attach to them and deliver drugs locally
- Gold-silica nanoshell particles that can kill cancer cells by heat when exposed to near-infrared light, or can be placed in immune cells that can cross the blood–brain barrier and target brain metastases, loaded with a drug that would be released by a laser
- A gold-coated magnetic particle that can carry a radioactive alpha emitter for close-range tumour targeting, and also limits emission of harmful 'daughter' products
- Nanodiamond particles for triple negative breast cancer – the particles are charged with a highly toxic drug, epirubicin, and targeted to the epidermal growth factor receptor (EGFR)
- A liposome nanoparticle containing arsenic trioxide that can preserve fertility in women treated for lymphoma
- An in-vitro test that can determine drug affects on fertility.

Stigma: breaking the vicious circle

ANNA WAGSTAFF

Stigma breeds silence, which fuels the fear and ignorance that feeds the stigma. Breaking this vicious circle not only makes life easier for people with cancer, but can also change public attitudes towards prevention and early detection, as some recent campaigns have shown.

"I learned that a person with cancer is a person and must be helped." This statement is one among many similar recorded in an impact assessment of a two-year campaign to change public perceptions of cancer, spearheaded by the LiveStrong foundation. It testifies to the success of the campaign, but it also speaks volumes about prevalent attitudes that many people will find all too familiar: being diagnosed with cancer leads some people to see you as less than the person you were; they may avoid you, or feel ill at ease with you, or even behave in a hurtful or discriminatory way.

This is stigma. It deeply unfair to people who already have a difficult disease to cope with. But stigma also plays a toxic role at a wider social level, helping make cancer and cancer patients invisible, stifling informed public discussion and perpetuating a cycle of fear and misinformation that blocks attempts to raise awareness about avoidable cancer risks and the importance of early detection.

Many people argue that policies and programmes to tackle this stigma – and the misinformation that it feeds off and perpetuates – are essential if we are to turn back the rising toll of suffering and death from cancer. Claire Neal, part of a team that heads up the LiveStrong anti-stigma campaign, is one of them. "Challenging stigma is a key that opens a lot of doors across the entire cancer control continuum," she says. "In our experience, if you can remove that barrier you can increase access to services and increase effectiveness of health promotion messages."

Why the stigma?

A few years ago, the LiveStrong foundation spent a year interviewing more than 4500 healthcare providers, cancer survivors, organisational leaders and community members across 10 countries, to learn more about cancer stigma and how it operates (*Cancer Stigma and Silence Around the World: A LiveStrong report*). They concluded that it is pervasive, existing across countries, cultures, and communities, and is characterised by a set of feelings, attitudes and behaviours, that they have compiled

into a universal "stigma index" that includes views such as:

- Treatment and support are useless for someone with cancer
- I would feel uncomfortable being friends with someone with cancer
- People can only blame themselves for getting cancer
- I would feel isolated/alone if I received treatment for cancer
- If my spouse had cancer, I would consider leaving him/her.

Neal believes there are a number of reasons why being diagnosed with cancer carries stigma in a way that, for instance, developing meningitis, measles or malaria doesn't. Cancers can affect a person in so many ways – how they look, how they feel, their sexuality, their ability to have children, and often relationships with friends and family. "There are so many ways that cancer and its treatment can impact a person's life, and there has been this silence around it," she says.

Uncertainty about how and why it develops is another factor. "Cancer is less well understood, because it is so many different diseases. Often we don't know exactly what causes it, and this can lead to different interpretations of what brings it on." In many communities it can be seen as the result of witchcraft, or a judgement from God, says Neal. In others it can be attributed to stress, to having a negative mindset or to failing to take proper care of one's mind and body. "Our research has shown that people often believe that people with cancer brought it on themselves, which again can be very stigmatising."

Fears that the disease may be infectious can result in people being shunned by friends and neighbours and

SHUTTERSTOCK

"Challenging stigma is a key that opens a lot of doors across the entire cancer control continuum"

Such negative beliefs, attitudes and behaviours can make people reluctant to 'admit' that they have cancer

excluded from the community. Fears that it is hereditary can ruin the marriage chances of those with a mother or father known to have had cancer. Whole families can find themselves impacted, which can then put intolerable strains on relationships, leaving people with cancer even more isolated. Stories of men walking away from marriages when their wife gets cancer – or vice versa – seem to be common across the globe; the concept of "relationship-toxicity" is now circulating among parts of the advocacy community as one of the common side-effects of cancer.

A cancer control issue

Not surprisingly, such negative beliefs, attitudes and behaviours can make people reluctant to 'admit' that they have cancer, or even that they are worried they may have cancer. They may be deterred from seeking professional advice about worrying symptoms or from attending screening – particularly if they are ill-informed about the value of picking up and treating cancers at an early stage. Another result, says Neal, is that it becomes very hard to challenge the stigma and misinformation, which then creates a vicious circle. "Because people feel stigmatised they don't want to talk about it. And in not talking about it, a lot of myths and misconceptions are increased and allowed to perpetuate."

Breaking that vicious circle by challenging myths about cancer was adopted by the International Union for Cancer Control (UICC) as its campaigning focus for this year's World Cancer Day. It was an interesting exercise, says Caroline Perréard, who played a key coordinating role, because myths are shaped by specific realities and cultures, and the campaign had to be relevant for all 760 member organisations in 155 countries.

UICC chose to focus on four myths:

- Cancer is a death sentence
- It is a matter of fate – nothing can be done about it
- It is a disease of the wealthy, elderly and developed countries
- It is only a health issue.

And they asked member organisations to identify the myths most relevant to them and to adapt the messages to their own needs.

It wasn't clear how effective this approach would be, not least because the countries most in need of promoting conversations about cancer myths would be those where the taboos and silence are strongest. "Working with different regions is very challenging, because there are different messages that we need to get across," says Perréard. "It's a learning curve. We want to aim messages to all regions of the world. But messages need to get to countries like Japan and Korea, for instance, where stigma is such a big issue that it is very hard to communicate about prevention or myths. People don't have access to the information."

Perréard was surprised by the feedback from member organisations. "They were really thrilled," she says. "They were so pleased to have a single theme they could all unite behind." Groups with a long track record of advocacy on stigma and myth-busting used World Cancer Day to stage rallies and capture the media spotlight. Groups that rarely venture into this territory took the opportunity to open conversations about the prevalence and nature of misconceptions about cancer in their communities, getting medical students to do interviews with one another and/or members of the public, which were then shared on YouTube or other social networks and used in press conferences. The authority given by this international focus helped create the conditions for survivors to break the silence and tell their stories, to show that cancer does not have to be a death sentence, that early diagnosis is important, and that even when it can't be cured, with treatment, care and support you can still have a good life.

An interactive map of events on the UICC's worldcancerday.org website gives an idea of the range of actions carried out around the globe. Click on Jeddah (west coast of Saudi Arabia), for instance, for an impressive example of how the UICC's global message was adapted to a local audience ("Myths and misconceptions about breast cancer", Wardi video).

More similar than different

Looking at the issues highlighted across the globe, it is the similarities that really stand out. People in developed countries may be less likely to blame witches, or even God, for their cancer, but they nonetheless show a strong tendency to distrust conventional medicine and turn to unproven and often irrational therapies when cancer strikes. And while progress in early diagnosis and treatment has reduced fear and stigma

Silent no longer. These people, and hundreds like them, have all challenged the taboo and stigma surrounding cancer by sharing their own stories on YouTube, Facebook and other social networks

LIVESTRONG

associated with breast and cervical cancer in countries with more developed health systems, the same cannot be said of lung cancer, which remains hard to detect in time even in richer countries, and still carries that burden of fear.

The vicious circle also seems to operate in a very similar way across the globe. A systematic review of the impact of stigma and nihilism on lung cancer outcomes, published in *BMC Cancer* in May last year, offers a pertinent example. It showed that perceptions that a diagnosis of lung cancer will inevitably result in death, and that cancer cannot be effectively treated, lead to delays in taking symptoms to the doctor or to refusing recommended treatments and investigations. Lung cancer carries a particular stigma due to its association with smoking, and the study found that this too could lead patients to delay reporting symptoms, because they believed that "treatment for lung cancer would likely be denied to smokers," or that they would be "blamed for their disease", even if they didn't smoke.

The study also found that patients' sense of being stigmatised acted as a deterrent to attending support groups – effectively leaving them silenced and invisible, and making it harder to challenge prevailing prejudice and convey potentially life-saving messages – the vicious circle at work again.

A joined-up approach

Further complicating this picture is the potential of anti-tobacco campaigns to reinforce this stigma, and thereby contribute to delayed diagnosis and added suffering for patients. A survey of attitudes towards lung cancer patients, conducted for the Global Lung Cancer

Looking at the issues highlighted across the globe, it is the similarities that really stand out

"The idea was that, if they got together to speak out, they could help reduce the fear and break the silence"

Coalition in 16 industrialised countries across five continents (Ipsos MORI 2011), showed the most negative attitudes were recorded in Australia – a country that has led the world in its efforts to tackle smoking – with 29% of respondents expressing agreement with the statement "I have less sympathy for people with lung cancer than people with other types of cancer." This compares with only 14% in Spain and 10% in Argentina (where the least negative attitudes were expressed). Evidence cited by the *BMC Cancer* study, meanwhile, indicates that some people with lung cancer see information campaigns on tobacco as "contributing to fatalistic views, as they focused on death rather than treatment" and that they feel the press reinforces the smoking-related stigma.

This potentially counteractive relationship between prevention and early detection messages may also work in the reverse direction: efforts to reduce the fear and stigma that can deter people from seeing their doctor need to take onboard the potential impact on prevention efforts. This seems to be the message coming out of a comparative study of perceptions of cancer in France and Morocco that was commissioned by the French Ligue contre le cancer and published to coincide with this year's World Cancer Day. The study showed that while French and Moroccans both associate "illness" and "death" with the word "cancer", the French respondents were far more likely to mention treatment, for instance "chemotherapy", while the Moroccans were more likely to talk in terms of a "danger", or a "red zone that must be avoided". However, the more positive French perception of the disease was accompanied by a far less accurate perception of lifestyle risks. More than 80% of Moroccans identified tobacco as the biggest cause of cancer, compared with less than 70% among French respondents, and while Moroccans put alcohol as the second most important avoidable risk factor (45%), French respondents put alcohol into fifth place at 31%, rating it as less important than pollution (38% vs 29% of Moroccans) and genetic factors (37% vs 23% among Moroccans).

Taken together, these findings indicate the need for a joined-up approach to cancer control where different aspects reinforce rather than undermine each other.

Breaking the vicious circle

Fighting stigma and fear is not traditionally a key component of national cancer control policies, but evidence of the impact where it has been done well suggests that perhaps it should be. The LiveStrong foundation recently completed two pilot anti-stigma campaigns – one in South Africa and one in Mexico – which hinged on giving cancer survivors a platform to tell their own stories. They seem to have achieved their objectives in the short term at least.

The impact assessment of the Mexican campaign showed that three out of four people exposed to the campaign learned something new about cancer; almost an equal proportion said they now talked more openly about cancer; and more than two in five said they did something different – in terms of protecting their own health and/or being more supportive to people with cancer – because of what they had learned.

Fernando Rodriguez helped organise the Mexican campaign. "At the beginning of the campaign, we had information from many different countries about why people don't receive the proper treatment on time," he says. "The problem is they never go for check-ups because they are afraid of learning they have cancer. Part of our objective was to try to change people's opinions. Instead of using awful numbers about all the people dying of lung cancer or prostate cancer or breast cancer, we tried to use the stories of all the survivors, from different social, economic and cultural backgrounds, and with different kinds of cancer. The idea was that, if they got together to speak out, they could help reduce the fear, break the silence and give different information through different approaches."

One thing they learned from survivors early in the campaign is that the fear and misperceptions are not only deterrents to early diagnosis, but also result in patients failing to complete their full course of treatment, "because they feel awful and feel it is part of dying a little bit." So the campaign tried to address this, says Rodriguez, by promoting the concept of 'the new normal'. "You will have critical changes maybe, but after the treatment you can have a new normal life. A lot of people say you have cancer, you are superhuman. No, I am not superhuman. I am different because now I can appreciate the

simple things of life. But you don't have to go down this path to learn to enjoy your life like me. That is part of the message from cancer survivors."

Focusing on four major cities in Mexico, they used radio, television, newspapers and, crucially, social networking. Two- to three-minute videos in which survivors from all ages and backgrounds gave their stories were uploaded onto the "Share your Stories" Facebook page. The site soon became a forum where survivors were able to interact with one another and upload their own videos. By the end of the campaign, the page was getting almost 900,000 visits per month.

In a stroke of genius, the campaign co-opted the support of Mexico's popular wrestling stars. They staged well-publicised events that started with the traditional good-guy-versus-bad-guy format. Two masked interlopers representing cancer would then enter the ring, and the good guy and the bad guy would team up to defeat them, with the whole crowd behind them. "The whole point was about the stigma," says Rodriguez. "The good guy and the bad guy were on the same team. Whether you are good or bad you are both wrestling the cancer."

Government support for the campaign, as an effective way to raise awareness about cancer and convince people to use the screening and treatment services available, was crucial. "People don't want to go because they are fearful and superstitious. We served as a link between those services and the public," says Rodriguez. Mobile screening clinics attended the public events, and people were also able to pick up tickets to attend clinics for check-ups. Where the results showed further investigations were needed, says Rodriguez, they were referred on to the relevant clinics or institutes.

The government also cooperated in an initiative to help health workers communicate better with patients and the wider public about cancers. This involved community health workers and hospital staff – nurses, admin workers, even oncologists. Now that the pilot is over, government and campaigners are keen to find ways to carry on work that they feel has proved so effective, says Rodriguez.

"We weren't sure if it would work, particularly as these were short-term campaigns," says LiveStrong's Claire Neal. "But we've been really encouraged to see that, yes, in a short amount of time, by elevating the voice of survivors, we were able not only to affect people's perceptions of cancer, but actually change what they did. More people were going to get screening, they were talking more openly about cancer, they were changing what they were doing as a result of these campaigns. We had hoped we would see perceptions shifting, but I think we found much more than that."

Most encouraging of all, says Neal, is the enthusiasm among participants to keep the campaigns going after the end of the formal pilot. "In both South Africa and Mexico local partners have said that they want to continue the activities of the campaign, and that they had reached populations they had never reached before."

In Mexico, Rodriguez is busy with a follow-up campaign based on photographs, called "Before cancer, After cancer", to carry the message that "the cancer could be another chapter in your life." He is also talking to the government about continuing support for the communication workshops, and maybe other parts of the campaign. "They want to encourage survivors to continue these activities, to speak out and share their stories of cancer. And at national level they are very interested in workshops for healthcare providers," he says.

LiveStrong is hoping the "stigma index" and the toolkit that they have developed will be used by groups across the world. "We see an incredible opportunity in this kind of work. If you can change how people view cancer you can really have an impact," says Neal. "What I think we've seen in the mental health community and HIV/AIDS and other areas where stigma is an issue is that often we focus solely or largely on access, but it has to be done at the same time as addressing stigma, because if there is this great stigma, people aren't actually accessing what's there. So the two have to go hand in hand."

The UICC also is keen to find ways to continue this work. The 16 member organisations that are on the Advisory Group that plans and organises World Cancer Day have agreed to stick to the same theme for 2014, focusing on new myths to dispel. Caroline Perréard is looking forward to it, saying the enthusiasm among the UICC members makes it the most exciting campaign she has worked on. ■

"Often we focus solely or largely on access, but it has to be done at the same time as addressing stigma"

Promoting new ways to control cachexia

MARC BEISHON

As new evidence shows we can do much more for patients at risk of cachexia, leaders in the field join forces in an ESO task force to spread the message.

Cachexia is one of the most distressing conditions for people with advanced cancer. Known also as wasting syndrome, about half of patients suffer from progressive loss of fat and muscle tissue, which often leads to severe emaciation and also death. For many years, cachexia has been seen by oncologists as an inevitable consequence of cancer, especially in solid tumours such as pancreatic, gastric and lung cancers. Management has been a question of monitoring weight and encouraging patients to eat anything they can – and of course attempting to treat the cancer – but there have been no single therapies that have worked.

That has not been for want to trying. As Vickie Baracos, professor of palliative care and an expert in cachexia and metabolism at the University of Alberta, Canada, recently reported in an editorial for the *Journal of Clinical Oncology* (1 April 2013), there have been about 100 randomised investigations of therapies for cachexia and anorexia, but most have been negative and none has resulted in an approved agent. A recent study on melatonin – which patients can buy over the counter – proved equally futile, though unlikely to do any harm. Cachexia is a widespread problem in cancer, but also occurs in other conditions such as heart disease, chronic obstructive pulmonary disease and AIDS, so the search for answers is pressing.

Now at last, 30 years since Baracos herself put forward some of the first evidence that inflammatory agents are implicated in muscle wasting, activity in this area is markedly increasing, raising hopes that effective ways of managing cachexia will be found. There are now several consensus groups, conferences and a society and journal on cachexia, a pipeline of new drugs in phase II and III trials, and a rapidly developing understanding of how studies can best be designed. As Baracos says: "The consensus building efforts herald a paradigm shift in the design of clinical trials."

While oncologists, and doctors in other specialisms where cachexia is seen, wait to see whether the latest drug therapies under investigation bear fruit, it is widely accepted that any new treatment is unlikely to amount to a 'magic bullet'. The recent consensus proposals and research strategies recognise that cachexia is not the same as malnutrition: it

Mark Washburn

is a complex, multifactorial metabolic condition that cannot be addressed with conventional nutritional support alone, and a medical therapy alone is also unlikely to be sufficient. Instead they point to new ways of classifying cachexia, and to 'multimodal' supportive strategies that could combine nutrition with drugs and also exercise. Crucially, there is emphasis on early intervention and possible prevention of cachexia. It is from this work that badly needed options may emerge for a patient group that is growing in number as the population ages.

Spreading best practice

Generally, early palliative involvement is proving to have better outcomes for patients with advanced cancer. However, the situation with cachexia today is that new strategies are being trialled only in a few pockets of excellence where there is already a strong focus both on cachexia and integrated palliative/supportive care. So most patients who develop cachexia are not yet being served better.

To more rapidly bridge the gap to the majority of cancer centres – to encourage the application of current knowledge and new evidence-based strategies – the European School of Oncology (ESO) has convened a cachexia task force that has awareness raising and implementation in its sights.

As task force member Stein Kaasa, professor of palliative medicine at the Norwegian University of Science and Technology, Trondheim, and chair of the European Palliative Care Research Centre, comments, there are two major interlinked reasons for assembling the task force. "The first is to define exactly what cachexia is, as it is not been clear to the cancer community, and we want to build on proposals for classification that have been put forward so far. Second, it is clear that much of the research and interventions that have been done are too late in the trajectory of the disease; when patients have late-stage cachexia there are no real effects of interventions. We are now understanding better the science about how and when cachexia starts, and what kind of earlier treatment we can offer to prevent or slow its development and help people live with better function and quality of life."

Both planks – classification and strategies for early intervention – are beginning to take shape, he adds, and some cancer centres have already set up cachexia clinics as part of supportive and palliative care. But most oncologists are still at square one in thinking about earlier, integrated intervention for cachexia. It is the aim of the task force, says Kaasa, to help turn existing and future knowledge into clinically

Crucially, there is emphasis on early intervention and possible prevention of cachexia

"It is very important that the oncology community has the optimal context in which to use these agents"

useful tools that can be applied outside of the specialist centres. To that end it is planning to publish a position paper on early recognition of cachexia.

Ken Fearon, professor of surgical oncology at the Western General Hospital, Edinburgh, Scotland, and ESO task force member, stresses the importance of defining cachexia in advance of applying new strategies. He is lead author of an international consensus paper on defining and classifying cachexia, and says the group is now working on validating this classification framework.

"In work led by Professor Baracos, we have been collecting large databases of patients according to variables that are thought to be important for the assessment of cachexia," says Fearon. "The data come from about 5000 patients at centres around the world, and two key variables we are looking at are percentage weight loss and BMI (body mass index), which when combined indicate the risk of early mortality. We now see there is up to a four-fold risk of shortened suvival depending on what weight loss and BMI are at the time of cancer diagnosis – that's really quite an amazing finding."

This is not the only definition and validation work – for example, another task force member, Federico Bozzetti at the University of Milan, with Luigi Mariani, had earlier put forward a proposal (see *J Parenter Enteral Nutr* 2009; 33:361–367).

The ESO task force members agree that there is more to come on defining cachexia, noting that weight loss alone as a criterion can conceal a disproportionately higher loss of muscle mass, and adding other factors including food intake and the presence of an inflammatory marker may more accurately capture the outlook for patients.

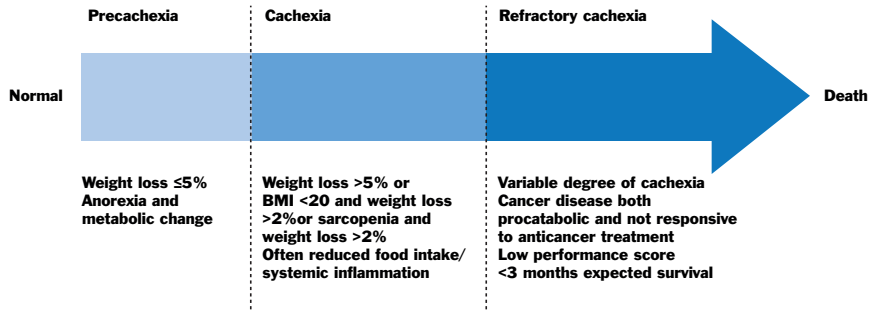
As Fearon adds, the key to understanding cachexia is not only recognising that it is a complex multifactorial problem, but also that it is a spectrum over time. "We now say that patients pass from an early indication, or precachexia, to cachexia, to becoming so moribund that they do not respond to any sort or treatment, i.e. refractory cachexia. It's an important message for oncologists – the classical view of cachexia is someone with severe emaciation who is about to die. Where we are moving to instead is cancer-associated weight or muscle loss, rather than just very severe cachexia – where the horse has already bolted."

There is added pressure on oncologists to understand cachexia better because of the large investment by pharmaceutical companies in new agents. "Some of these are in phase III trials and could report positive in the next year, and it is very important that the oncology community has the optimal context in which to use these agents," says Fearon. "This involves providing the best treatment and care – what goes on in the background before you use a new drug."

A multimodal approach

This is where a multimodal strategy for earlier intervention comes in, and there is a key trial that task force members are involved in and watching closely. The MENAC trial – Multimodal Exercise–Nutrition–Anti-inflammatory treatment for Cachexia – is designed to combine nutritional support with aerobic exercise and an anti-inflammatory drug (celecoxib), says Kaasa. "We have already piloted this approach in 40 patients and are now organising a multicentre study that will enrol patients when they start chemotherapy, to compare them with 'business as usual',"

Definition and classification: towards an international consensus



Source: K Fearon, F Strasser, SD Anker et al. (2011) *Lancet Oncol* 12:489–95, reprinted with permission from Elsevier

he says. "It will be a true collaboration between medical oncology and palliative care. We will be looking for prevention of cachexia, better quality of life and physical function for a longer time, and even better tolerance of chemotherapy." Funding though could be a challenge, and the group will be looking for contributions at national level for the 15 centres that will run the full MENAC study.

As Fearon adds, the study could also highlight the effect that support measures can have on drug therapy. "As some drugs are not very potent, their effect may be doubled if you are sensible about the supportive background in which you use them," he says. "In any case, the best way to attain muscle mass is to exercise. It's madness for oncologists not to tell patients who have muscle wasting that they should be going out for a walk every day.

"It's all about treatment and care for cachexia right from the time of diagnosis, particularly with advanced cancer. We also know that neoadjuvant and palliative chemotherapy is associated with cachexia, so maintaining patients during treatment is another focus for the future, and why the task force is so important – we need to get medical oncologists to think about this problem more proactively."

Kaasa says the work of the task force is being well-publicised at various meetings, such as at the Multinational Association of Supportive Care in Cancer (MASCC), which took place in Berlin in June, at ESMO next year, and at specific cachexia events. He summarises the agenda: "First we need to come up with a consensus on the content of the classification system. Then we need to operationalise it into a practical tool that can be tested in the clinic. That's the diagnostic track. We need to watch carefully the studies run by the industry on new drugs, while running our MENAC study on multimodal intervention – the trial is a particular priority for us. And we need to further develop the basic science and encourage better collaboration with clinicians to understand more about cachexia and also to find biomarkers to classify the patient in addition to the indicators we are developing in our clinical classification system."

The ultimate aim – as with so much in cancer – is personalised treatment and support at the point at when it can make a difference. ■

Personalised cancer care: where do we stand today?

Since the concept of personalised cancer therapies first emerged, the picture has become so much more complex and challenging. The co-director of MD Anderson's Khalifa Institute for Personalised Cancer Therapy presents the state of current knowledge and charts the way forward.

> *"If it were not for the great variability between individuals, medicine might as well be a science, not an art."*
> Sir William Osler (1892)

The whole concept of personalised medicine is not really new. We've been treating patients in a personalised manner for many years; the change is in our ability to understand what we are doing and how we deliver personalised medicine, hopefully leading to improved outcomes.

We are now able to characterise and study each patient and their tumour in a breadth and depth not previously possible, which allows us to be much more precise in the way we manage the individual. I want to change the mantra of personalised medicine – 'the right dose of the right drug for the right indication for the right patient at the right time' – to add 'the first time'. It's become clearer that the first time we get to challenge

European School of Oncology e-grandround

The European School of Oncology presents weekly e-grandrounds which offer participants the chance to discuss a range of cutting-edge issues with leading European experts. One of these is selected for publication in each issue of *Cancer World*. In this issue Gordon Mills, of MD Anderson's Khalifa Institute for Personalised Cancer Therapy in Houston, Texas, provides an update on the challenges and opportunities in personalised cancer medicine.

Daniel Helbling, from the Gastrointestinal Tumour Centre in Zurich, Switzerland, poses questions arising during the e-grandround live presentation.

Edited by Susan Mayor.

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

the tumour with therapy is the most important time in determining the patient's outcome, so one of the key goals is give the right treatment first.

In the past, we treated cancer patients with relatively blunt instruments – chemotherapy, radiation therapy – that target primarily the proliferative rate of the tumour. We can now begin to characterise tumours in sufficient depth to identify what drives the tumour and then to target that in a way that capitalises on the changes in the tumour. Normal cells are incredibly robust. In contrast, cancer cells are genomically unstable and have many aberrations, which in many cases render the cancer cell less robust than normal cells in the body. If we can understand these dependencies it should be possible to define approaches that more selectively target and kill tumour cells.

It's an incredible time. With new technologies and approaches we finally have the ability to let the patient teach us what is important. We have what we hope is a 'perfect storm' of two events coming together: the ability to characterise the patient and the tumour on the one hand, and an incredible repertoire of drugs able to capitalise on the genetic changes present in the patient's tumour on the other. There are almost 1000 different drugs in, or about to enter, clinical trials that target particular underlying events in tumours, including more than 100 in breast cancer alone.

Using response prediction biomarkers

The most effective targeted agents are linked to response prediction biomarkers (see table below). With these, we are seeing remarkable responses in patients in a range of different cancers. The good news is that there are more and more of these. The bad news is that, in many cases, it takes far too long from when we identify underlying abnormalities to when we move a drug into the clinic.

Crizotinib represents what we hope will be the new approach. It took less than four years from identification of a particular abnormality in lung cancer – EML-4 ALK fusion gene – to a drug being shown to be effective in clinical trials and approved for use in this disease, for which we had no other therapy option that worked. Crizotinib was being developed for a completely independent reason. However, it was known to target ALK, and because it was available on the shelf, ready to go, it was very easy to link testing for the EML-4 ALK aberration that occurs in a subpopulation of lung cancer to treating patients with a drug specifically targeting that therapeutic liability.

In the past, our drug development pipeline has been full of failures. The success rate from phase I to approval in the US in cancer drugs is around 5%. We clearly need to change the way we are doing things. One of the key steps in that process is linking biomarkers that can be used to identify patients likely to benefit to the incredible toolbox of targeted agents. Hopefully, we are entering an era where we can do this much more efficiently and get effective drugs to our patients. For BCR-ABL, identification through to an approved drug took over 40 years. erbB2 inhibition took 13 years, and evaluation of PARP inhibition is still ongoing for BRCA1 and BRCA2 mutation carriers. But for BRAF, identification of the abnormality to an effective targeted therapy took 8 years and crizotinib for EML-4 ALK took only three to four years.

TOOLBOX OF TARGETED THERAPIES

Imatinib mesylate	CML	BCR-ABL translocation	Oncogene addiction (1982)
Imatinib mesylate Sunitinib Nilotinib Dasatinib	GIST Dermatofibrosarcoma protuberans Hypereosinophylic syndrome Melanoma	c-KIT mutation PDGFR mutation	Oncogene addiction (1999)
Trastuzumab Pertuzumab Lapatinib	Breast	HER2 amplification	Oncogene addiction (1985)
Gefitinib, Erlotinib Cetuximab	Lung cancer Bowel	EGFR mutation	Oncogene addiction (2004)
Midostaurin, Sunitinib, CMT53518	AML, ALL	FLT-3 mutation, tandem duplication	Oncogene addiction (1996)
PARP inhibitors	Breast Ovarian	BRCA1/2 mutation	Synthetic lethality (2005)
Vemurafenib	Melanoma	BRAF (8 years)	Oncogene addiction (2002)
Crizotinib	Lung	EML-4 ALK (4 years)	Oncogene addiction (2007)
Ibrutinib	CLL	BTK expression	Lineage (1993)
Tamoxifen, AIs	Breast cancer	ER expression	Lineage (1800s)

Most effective targeted agents (with the exceptions of VEGFR and proteasome inhibitors) are linked to response prediction biomarkers; one of the big challenges is to shorten the time from identifying a potential therapeutic target to getting a therapy into the clinic

Source: Courtesy of Gordon Mills, MD Anderson Cancer Center, Houston, Texas

The MD Anderson Cancer Center approach

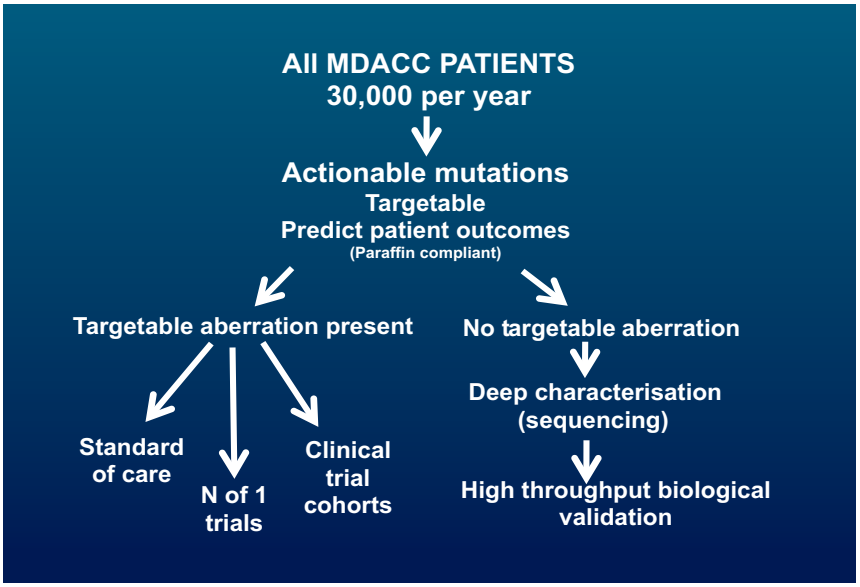
The way we run projects at the MD Anderson Cancer Center provides a model for how we might move this personalised approach forward (see figure *right*). Within five years, for all patients likely to enter clinical trials – totalling 30,000 per year, making this a major challenge and opportunity – we plan to characterise all of the actionable aberrations using multiple platforms looking for anything where we have a potential drug or where we can predict patient outcomes. If there is a targetable aberration, we will direct patients to the standard of care where this is available – for example erbB2 amplification targeted therapy in breast cancer – or to clinical trial cohorts, filling them at a rapid rate and so helping to get more effective drugs to patients. Patients with rare events will be offered '*n* of 1' trials of therapy (where they are the only trial subject) related to what is going on in their tumour.

Many patients – more than half – have no targetable aberration present. We then propose to characterise what is going on in much greater depth to try to understand targets that we haven't previously looked at, and determine whether the patient can benefit from them.

How this can work: the PI3K pathway

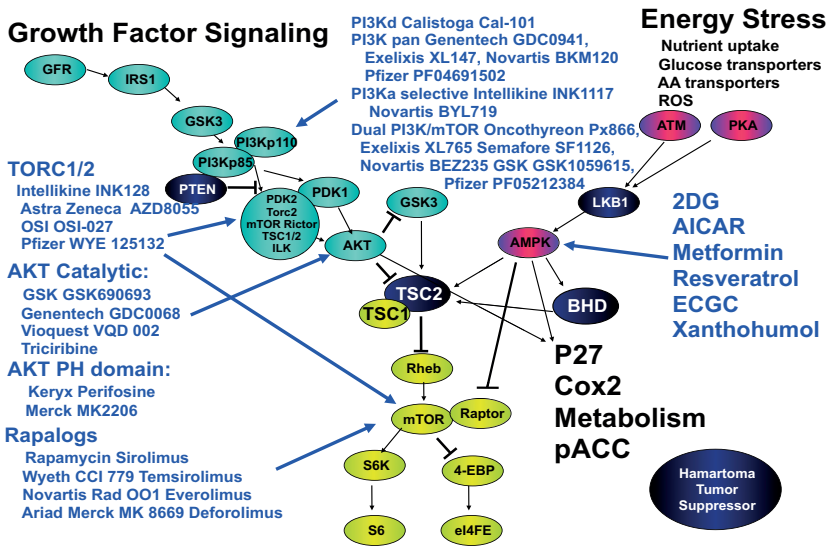
The PI3K pathway is proving critically important. We have more mutations in this pathway and more patients that we can target with current therapies than for any other pathway. A wide range of drugs targeting the PI3K pathway are currently in clinical trials (see figure *right*). Where there is a good toolbox of therapies, the challenge is to identify patients that may benefit.

A MODEL APPROACH



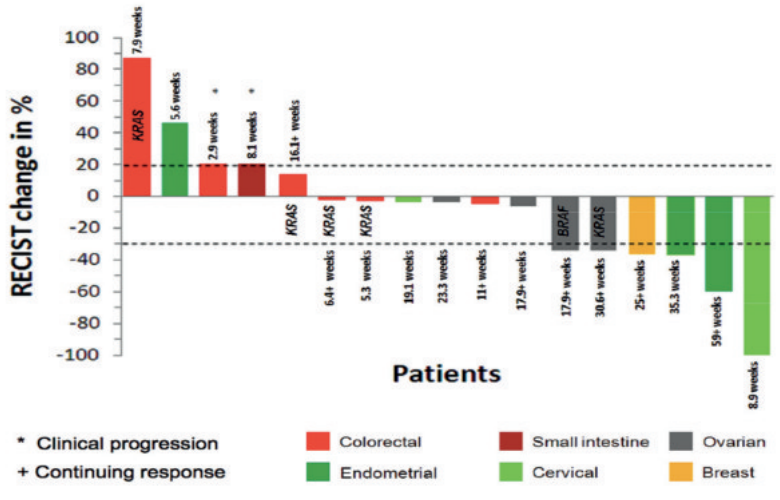
The MD Anderson Cancer Center (MDACC) systematically screens the tumours of all its patients for targetable aberrations, directing them into trials or further sequencing as appropriate

PI3K TARGETED THERAPIES



The PI3K pathway, which integrates growth factor and energy/stress signaling that play a role in protein synthesis, cell growth, cell survival, cell cycle progression and motility, has multiple targets for which therapies are already available

RESPONSE TO PI3K TARGETED THERAPIES



These phase I results show highly unusual response rates of 30% in patients with PIK3CA mutations; however, benefit varies according to tissue type and co-mutation

Source: F Janku, AM Tsimberidou, I Garrido-Laguna et al. (2011) *Mol Cancer Ther* 10:558–565, reprinted with permission from AACR

The figure above shows data from the MD Anderson phase I programme for patients with mutations in a single gene (PIK3CA) to therapies targeting this pathway. More than 30% of patients are demonstrating benefit, based on RECIST criteria, which is almost unheard of in a phase I programme. Cancers including cervical, ovarian and breast, shown on the right of the waterfall plot, benefited markedly, while other cancers including colorectal, shown on the left-hand side, do not seem to benefit, for reasons that are not yet clear.

We predicted that co-mutations in the RAS pathway would be markers for resistance but, surprisingly, while RAS mutations in colorectal cancer appeared to confer resistance, two patients with ovarian cancer with mutations in this pathway demonstrated RECIST criteria responses. What does this mean? We believe that linking aberrations to targeted therapy is going to work, but having markers of sensitivity – PIK3CA mutations – is not enough. It will be contextual on the intrinsic gene expression pattern in the patient's tumour and co-mutations in the tumour.

Many years ago I proposed that we would have RAS clinics for all patients with RAS aberrations. Looking at our data, and that of many others, we are now thinking of RAS in the context of a specific disease, and – managing patients in a disease-oriented programme with an overlay of the genetic aberrations that can be targeted.

Challenges in personalised therapy

The idea of using personalised therapy and being much more effective sounds wonderful. But there are a lot of challenges to be overcome:

How personalised?

Can we really provide a specific therapy for every single patient? This is an anathema to regulatory agencies that want large-scale trials to show improvement in outcomes with a specific drug in a specific disease.

What we are probably going to be doing for a while is precision or stratified medicine: finding homogeneous groups with a particular set of aberrations that are likely to benefit from a particular therapy.

But even that comes with a problem. For example, breast cancer – the most common cancer – has at least eight independent, therapeutically relevant subclasses. One of these is so small that we are unable to mount clinical trials without massive consortia and many years of intervention.

Trials for rare aberrations

Some of these aberrations are quite rare. AKT mutation is one of the key aberrations in the PI3K pathway, but it occurs in about 0.7% of patients going on clinical trials. This means testing thousands of patients to find sufficient patients with this aberration to complete a single trial. Multiplex testing for many different genomic aberrations can direct patients to many different studies, including those for rare aberrations such as AKT mutation.

Small tumours

Obtaining sufficient tissue to test can be challenging with small tumours.

Understanding resistance

Responses tend to be short. We do not understand why resistance emerges in most of the cases, but are attempting to understand this in order to develop rational combinatorial therapy, which will be critical to moving ahead.

We know that positive predictive

markers can have only a modest predictive value – only 30–60% of patients with the dominant marker of HER2 amplification benefit from therapy targeting HER2. The rest do not, and we don't understand why. Unfortunately, when we have a negative predictor such as RAS mutation, it appears dominant over sensitivity.

Side-effects

The pathways that are abnormal in most cancers are the same pathways that function in normal cells, and the question is: can we develop sufficient therapeutic index for targeted therapies to benefit our patients?

Collaboration

How are we going to deal with these major challenges to the field? We are going to need a broad programme – collaborating across many different institutions – where we are able to identify the genomic events driving tumour progression, a repertoire of drugs, biomarkers for individuals likely to benefit, and rational combinatorial therapy.

Pilot project T^9

MD Anderson's T^9 pilot project – short for Ten Thousand Tumours, Ten Thousand Tests, Ten Thousand Therapies – is analysing the cancer-causing genetic variations in the tumours of 10,000 patients with advanced cancers that have no standard therapy. Data from the first 1000 tumours analysed in depth showed the frequency of mutations was lower than we had expected: less than 50% of patients had an actionable mutation. There were lower than expected numbers for many of the actionable mutations, which will be important in the design of clinical trials, as it will be necessary to test many more patients than originally predicted.

A facilitation programme, Clearinghouse, which is run through the Institute for Personalised Cancer Therapy (IPCT), helps the faculty at MD Anderson drive clinical trials. A physician contacts us about any patient who is likely to enter a clinical trial – we now have more than 1400 patients enrolled, recruiting more than 300 patients a month. Tissue is obtained and directed to our CLIA laboratory (CLIA indicates its meets Clinical Laboratory Improvement Amendments standards), where it is tested for more than 400 aberrations that are important as targeted events. This is being expanded to an even broader protocol. We also analyse samples for many more events in a research laboratory, giving us an incredible repertoire, speed and cost advantage to be able to identify potential driver aberrations.

Aberrations are reported back to the faculty, following confirmation in the CLIA laboratory, and they use this information to fill their clinical trials, with umbrella or bucket trials, where we may have five or 10 different therapies for different aberrations, and also to direct patients to *n* of 1 trials. Decision support is provided by a tumour board, and data capture of mutation frequency and outcomes determines that this is truly benefiting patients.

A single patient can change the way we manage cancer

In any clinical trial 5–10% of patients demonstrate remarkable responses, and these patients can teach us important lessons. For example, we started a trial some time ago with sorafenib, meant to target BRAF, which was known to be important in melanoma. One patient responded dramatically. After two months, their melanoma had disappeared completely and has not returned 11 years later. However, we characterised BRAF and found absolutely nothing going on. Looking more deeply, we found a causal mutation in KIT, another actionable oncogene. Based on this plus other data, we now test all patients with acral, mucosal and chronic skin-damaged melanoma for KIT mutation and direct them to KIT-targeted therapy (*Nature Clin Practice Oncol* 2008, 5:737–740). This accounts for about 30% of acral, mucosal and chronic skin-damaged melanoma. This was a change in practice driven largely by a marked response in one patient, and letting that patient teach us what was important.

Deep molecular characterisation of each of a patient's aberrations is needed to determine which are drivers and what is the best therapy to target these drivers. This whole idea of deep characterisation of every patient with an underlying mutation or response, to try to determine the best approach, is now emerging as the standard at our institution.

Intratumoural heterogeneity

There is marked heterogeneity in many patient tumours, with intratumoural heterogeneity within a single tumour and marked heterogeneity between primary tumours and metastases. These can be pre-existing, in the primary tumour that seeds the metastases, or due to further evolution after the metastasis has occurred.

How are we going to manage this complex problem of intratumoural heterogeneity? It is important to do multiple biopsies – trying to capture both spatial and time-dependent heterogeneity. Currently, we believe our best approach is to treat the dominant mutation we find. If the patient benefits and then recurs, we need to re-biopsy to see what has changed and what is now the dominant clone that we should treat. For example, in breast cancer we re-biopsy patients when they recur to inform us of the best therapy.

The next step is going to be to move from biopsy to looking at circulating DNA and circulating tumour cells. From our early data we believe they will reflect what is going on in all metastatic sites in the body, giving us a much better way to determine what is the best next treatment for the patient. In our preliminary studies on this, when we know what we are looking for in PIK3CA studies, we have 80–90% concordance between what we find in the blood and what we find in the tumour.

Once we have detected an aberration is a driver, what do we do about it? A recent study showed that not all KIT mutations are equal. About 16% of patients who had abnormalities in KIT had clear responses. However, looking much more carefully showed they fell into two groups. There were those where there was evidence that it was a driver mutation and altering the tumour's behaviour – recurrent mutations that were functionally important. This study identified KIT mutations K642E and L576P in this group – 40% of patients in this population responded, which included all of the responders to imatinib. The other group comprised mutations seen only once, which were not drivers and did not signal sensitivity to the drug. The lesson from this is that it's important to know whether a gene is mutated, but it's also critically important to know whether the mutation drives the behaviour of the tumour, rendering it sensitive to therapy.

Looking to the future, we will need to carry out multiple biopsies, characterising the primary tumour and metastases in sufficient depth to identify subclones before carrying out a trial of therapy targeting the dominant subclone against which we have active drugs. Hopefully the patient will respond and sometimes they will be cured. If they recur, we need to re-biopsy and determine what has changed and what is now the current driver to guide a new round of therapy. If we can convert cancer into a chronic disease with relatively benign therapies we should greatly improve morbidity and mortality for our patients. ■

Question to the live webcast participants:
Do you re-biopsy patients at your centre?

One-third said they never re-biopsy; two-thirds re-biopsy in up to 30% of patients

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Post-traumatic stress disorder – prevalent and persistent

OKANA PALESH AND CHERYL KOOPMAN

Post-traumatic stress disorder (PTSD) is prevalent in patients with breast cancer, and African American, Asian and younger women are disproportionally affected. PTSD is associated with adverse effects on psychological and physical health and might be an indicator of other risk factors. It is important to screen and treat for PTSD, and more research is needed.

This article was first published in ***Nature Reviews Clinical Oncology*** vol.10 no.5, and is published with permission. doi:10.1038/nrclinonc.2013.49

Receiving a diagnosis of breast cancer is likely to have a considerable impact on the psychological wellbeing of the patient. In a recent observational study, Vin-Raviv et al.[1] reported that 23% of 1139 women with newly diagnosed localised breast cancer experienced post-traumatic stress disorder (PTSD) symptoms. Although the PTSD symptoms decreased over time, 16.5% had PTSD at first follow up (4 months after diagnosis); 12.6% had PTSD at the second follow up (6 months after diagnosis), and a minority of patients (12.1%) experienced persistent PTSD (defined as having PTSD at two consecutive interviews). Among these patients with breast cancer, African American and Asian women experienced disproportionally more PTSD when compared with white women. Indeed, African American women were 48% more likely to have PTSD than their white counterparts, and this difference was even more pronounced for Asian women with breast cancer, who were 69% more likely to have PTSD compared to white patients. Furthermore, younger women (<50 years of age) were significantly (P<0.01) more likely to report PTSD compared to older women.

PTSD as a psychiatric diagnosis describes a pattern of distress response experienced by some individuals in the aftermath of a traumatic event. PTSD was originally observed in the military context, but more recently it has been recognised in the context of serious medical illness.[2] Individuals diagnosed with PTSD suffer from three types of symptoms: intrusive distressing thoughts and feelings related to the event (such as distressing flashbacks of receiving the cancer diagnosis); persistent emotional numbing and avoidance of reminders of the traumatic event (for example, feeling emotionally distant from loved ones); and increased hyperarousal (such as difficulty falling or staying asleep).[2] Life-threatening illnesses, such as cancer, pose unique risks for PTSD compared to most types of time-limited traumatic events, such as military combat, rape, or accidents.[3] Much of the traumatic stress associated with cancer is focused on future threats (such as recurrence) rather than on past events. Furthermore, the experience of having cancer poses a risk of cumulative trauma due to uncertainties regarding recurrence, metastases, and shortened survival rather than the reliving of a singular traumatic event.[3]

It is remarkable that Vin-Raviv et al.[1] found that almost a quarter of women recently diagnosed with breast cancer had PTSD, considering that in the general US adult population the lifetime prevalence of PTSD is approximately 8%.[2] Perhaps, this high prevalence of PTSD can be attributed to cancer-specific characteristics – it is not only a life-threatening illness, but also an illness in which the threats of recurrence, metastases and untimely death are always present. In addition, cancer treatments are noxious because they create numerous adverse effects that unfold over months and even years. In previous research, having more post-surgical treatment was associated with greater PTSD symptoms in women with

recently diagnosed localised breast cancer.[4] In women with metastatic breast cancer, the incidence of PTSD was 52%,[5] more than double the 23% found among women with localised breast cancer in the present study. Although the latter study[5] focused on women who were seeking help for their psychological distress, it underscores the potentially traumatic nature of metastatic breast cancer.

PTSD is an indicator of psychological vulnerability that can also signal the presence of other adverse health-related characteristics, such as low socioeconomic status and poor physical and mental health-related quality of life.[6] In patients with breast cancer, those who have PTSD are also more likely to have other current or past psychiatric disorders and prior history of violent trauma.[6] In addition, it is also associated with greater functional impairment, such as employment absenteeism.[6] There is considerable evidence that PTSD contributes to worse health outcomes via multiple pathways.[7] These pathways include: greater health risk behaviours (for example, smoking); biological alterations (such as deregulation of the hypothalamic–pituitary–adrenal axis); psychological alterations (including depression); attentional processes (for example, altered pain perception); and illness behaviour (such as health-care utilisation) – all of these behaviours have the potential to contribute to greater morbidity and shorter survival.[7]

A major strength of the present study[1] is its large, ethnically diverse and multicentre sample, which enabled the examination of racial disparities in PTSD. The finding that a greater percentage of African American women than white women had PTSD is notably similar to a finding in men with prostate cancer.[8] Furthermore, the present study found that Asian patients were also more likely to have PTSD than white patients with breast cancer. The authors of the study appropriately point out that minority ethnic group status is often associated with risk factors that might help to account for the development of PTSD (for example, less access to medical treatment).[1] Specific cultural characteristics, such as greater stigma associated with medical illness, might also help to explain the racial differences in PTSD, although further investigation of such possibilities is necessary.

Increasing attention is being directed towards addressing patients' needs for psychosocial care. The National Comprehensive Cancer Network (NCCN) has established clinical guidelines for identifying, referring, and treating distressed patients with cancer.[9] The NCCN guidelines constitute a major step forward in addressing these needs. Although the guidelines do not specifically address PTSD in cancer, they lay the foundation for developing a framework to ameliorate distress in patients with cancer. Going forward, it is important to consider how these guidelines can be applied and provide the bridge for further efforts to treat and address the needs of patients with cancer who have PTSD.[9] Interventions that are easily accessible might be particularly attractive to this population given the high burden of cancer treatments. For example, in a previous randomised clinical trial, a web-based support group demonstrated efficacy in reducing PTSD symptoms in women with primary breast cancer.[10]

PTSD is prevalent and persistent in a significant minority of patients with breast cancer; thus, patients should be screened and treated for PTSD. The burgeoning literature on PTSD and other forms of impairment[1,4–6] associated with breast cancer is consistent with the study finding suggesting that younger women have higher levels of symptomatology, underscoring the importance of screening younger female patients with breast cancer for PTSD. Although, pharmacological and behavioural treatments have been used successfully in veterans, patients with HIV, and other trauma survivors, very few treatments are designed to be implemented in patients with breast cancer who are in active treatment. It is important to treat symptoms of any disorder early to prevent the development of chronic problems and to ameliorate distress associated with having a cancer diagnosis. The types of psychological treatment should vary according to the intensity of co-occurring medical treatment. For example, during active medical treatment, brief tailored behavioural interventions such as stress management training should be the primary focus, whereas during the survivorship phase, more-intensive psychological treatments are warranted (for example, supportive and cognitive behavioural therapy).[3] ■

Key point

It is important to recognise that a substantial minority of women will experience post-traumatic stress disorder symptoms related to their diagnosis and treatment of breast cancer, with African American, Asian and younger women particularly vulnerable.

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Acknowledgements
This research was supported by funds from the National Cancer Institute K07CA132916 and the California Breast Cancer Research Grants Program Office of the University of California, Grant Number 17AB-1600

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

newsround

Selected reports edited by Janet Fricker

ABVD less effective and more toxic in older patients

■ Journal of Clinical Oncology

In patients aged 60 years or older with Hodgkin lymphoma (HL), four cycles of ABVD is associated with substantial toxicity, resulting in grade 3–4 toxicities in more than two-thirds of them, a German study has found. Older patients are also more likely to experience dose reduction, treatment delays and treatment-related mortality.

Approximately 20% of all patients with Hodgkin lymphoma are aged over 60, and ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy is regarded as standard of care for these patients. Little is known, however, about the feasibility and efficacy of ABVD in this age group.

In the current study, Peter Borchmann and colleagues from the University Hospital of Cologne, Germany, compared the feasibility and efficacy of four cycles of ABVD in patients aged 60 to 75 years with early-stage Hodgkin lymphoma, who were treated within the German Hodgkin Study Group (GHSG) HD10 and HD11 trials, with that of younger patients (defined as under 60 years).

HD10 randomly assigned patients with early-stage, favourable Hodgkin lymphoma to two or four cycles of ABVD and then 20 Gy or 30 Gy of involved-field radiotherapy (IFRT); while HD11 randomly assigned patients with early-stage, unfavourable/intermediate disease to four cycles of ABVD versus BEACOPP and 20 Gy versus 30 Gy IFRT.

To achieve a more 'homogeneous' group, the authors combined and analyzed patients from both studies who had received four cycles of ABVD followed by either 30 Gy or 20 Gy IFRT.

In total, 1299 patients received four cycles of ABVD; of these, 117 were 60 years or older (median, 65 years). In 16 of these older patients (14%), treatment was not administered according to the protocol, mainly due to excessive toxicity. The mean treatment delay was 2.2 weeks for older patients, versus 1.2 weeks in younger patients.

Of the older patients, 59% achieved a relative dose-intensity of at least 80%, compared with 85% of younger patients.

WHO grade 3 and 4 toxicities during chemotherapy (including leucopoenia, nausea, and infection) were documented in 68% of older patients versus 50% of the younger group. Grade 4 toxicities were seen in 18% versus 7% ($P<0.001$), and treatment-related mortality was 5% versus 0.3% ($P<0.001$).

In terms of efficacy, the complete remission rate was 89% in the older group compared to 96% in the younger group ($P=0.006$), five-year progression-free survival was 75% versus 81% in the younger group, and overall survival at five years was 90% in the older groups versus 97% in the younger group.

"These findings challenge ABVD as standard treatment and underscore the necessity to develop treatment strategies suited for the specific needs of older patients with HL," write the authors.

In an accompanying commentary, Andrew Evens, from the University of Massachusetts Medical School, Worcester, Massachusetts, and Fangxin Hong, from the Dana-Farber Cancer Institute, Boston, Massachusetts, write that the first step to improve outcomes should be to design clinical trials specifically for older patients. "Multicenter collaborations that integrate novel agents and incorporate formal assessments of functional status to tailor therapy on a patient-specific basis will be critical to the successful study of and improved outcomes for older patients with HL," they write.

■ B Böll, H Görgen, M Fuchs. ABVD in older patients with early-stage Hodgkin lymphoma treated within the German Hodgkin Study Group HD10 and HD11 Trials. *JCO* 20 April 2013, 31:1522–29

■ A Evens, F Hong. How can outcomes be improved for older patients with Hodgkin lymphoma? *ibid* pp1502–05

Axillary node dissection can be avoided in patients with limited sentinel node involvement

■ Lancet Oncology

The International Breast Cancer Study Group (IBCSG) 23-01 study found no adverse effect on survival when axillary node dissection was avoided in patients with early breast cancer and limited sentinel node involvement.

For patients with breast cancer and metastases in the sentinel nodes, axillary dissection has been standard treatment. Recently, however, concerns have been voiced that, for patients with limited sentinel-node involvement,

axillary dissection might represent overtreatment, with side-effects including lymphoedema, pain and reduced arm movement.

In the current study, Viviana Galimberti and colleagues, from the European Institute of Oncology, Milan, Italy, set out to determine whether no axillary dissection was non-inferior to axillary dissection in patients with one or more micrometastatic (≤2 mm) sentinel nodes and tumours of maximum 5 cm. Altogether, 6681 patients from 17 centres were screened for enrolment, with only 934 (14%) meeting the requirement of micrometastatic sentinel nodes. Between April 2001 and February 2010, the 934 patients were randomised 1:1 to either axillary dissection (*n*=464) or no axillary dissection (*n*=467).

At a median follow-up of five years, disease-free survival was 84.4% in the group with axillary dissection versus 87.8% in the group without (*P*=0.16). Furthermore, the five-year cumulative incidence of breast cancer events was 10.8% in the group with axillary dissection versus 10.6% in the group without axillary dissection (*P*=0.90).

In the group that underwent axillary dissection, grade 3–4 long-term surgical events included one of sensory neuropathy, three of lymphoedema, and three of motor neuropathy. In the group without axillary dissection one grade 3 motor neuropathy was reported. Accrual was slower than anticipated, mainly because small metastases were rare.

These findings, write the authors, are consistent with the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial in 2011, which randomly assigned 856 patients with limited macrometastatic sentinel node involvement (not more than two metastatic sentinel nodes) to axillary dissection versus no further axillary treatment. After 6.3 years the ACOSOG Z0011 trial found the groups showed no differences for any endpoints.

"It is possible that our trial and ACOSOG Z0011 will change clinical practice, sparing many patients with early breast-cancer axillary dissection, especially when the sentinel node is minimally involved, thus reducing surgical complications related to axillary dissection with no adverse effect on survival," write the authors.

Already, they add, the 2011 St Gallen Consensus Conference has moved in the direction of recommending that micrometastases in a single sentinel node should not be an indication for axillary dissection irrespective of the type of breast surgery given. In an accompanying commentary, John Benson, from Cambridge University Teaching Hospitals Trust, UK, writes: "These results of IBCSG 2301 are practice changing when co-interpreted with those of Z0011."

■ V Galimberti, B Cole, S Zurrida et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. *Lancet Oncol* April 2013, 14: 297–305

■ J Benson. Management of breast-cancer patients with sentinel-node micrometastases. *ibid*, pp 266–267

Questionnaire explores patient reluctance for RCTs

■ British Journal of Cancer

Altruism, and the belief that trials offer the best available treatment option represent the top reasons patients decide to enter into randomised clinical trials (RCTs), a UK study has reported.

Worldwide recruitment into RCTs has remained fairly low, impeding the early introduction of efficacious treatment into clinical settings. Understanding some of the reasons why patients reject participation in trials is considered useful to inform future patient communication and trial design.

In the current study, Val Jenkins and colleagues from the University of Sussex, Brighton, UK, administered two questionnaires, each with 16 questions, to examine the reasons why patients accepted or declined trial entry.

The first questionnaire examined reasons why patients accepted or declined trial entry, with the initial question establishing whether or not they had agreed to trial entry. The second questionnaire explored patients' perceptions about their healthcare professionals' information giving, with the initial question addressing who had spoken with them about the trial (e.g. research nurse or clinician).

For each statement, patients registered their agreement on a scale of 0 to 4 (0=strongly agree, 1=agree to some extent, 2=unsure, 3=disagree to some extent, 4=strongly disagree). Both questionnaires were given to patients by research nurses, with patients completing the answers at home once they had decided whether or not they would take part.

Questionnaires were completed by 358 out of the 486 patients approached (74%). The responses showed that 291 (81%) had joined a RCT while 56 (16%) had declined and 11 (3%) were undecided. The primary reason given for trial acceptance was altruism (40%; 110/275), followed by the belief that the trial offered the best treatment (18%; 50/275). The main reasons given for declining the trial were trust in the doctor (28%;12/43) and wishing the doctor to choose (14%; 6/43).

A noteworthy finding was that 44% of responders declining trials (20/45) had been offered a trial comparing standard treatment with novel drugs or different durations of standard treatment.

Patients indicated that trials were discussed more often by research nurses (65%; 224/345) than clinicians (29%; 101/345) or both (6%; 20/345). Communication was good, with 97% of trial accepters and 100% of trial decliners saying their healthcare professional used clear and understandable language; 99% of accepters and 100% of decliners understood that trial entry was voluntary.

"These findings present a very positive picture of the communication received by

patients in the United Kingdom about clinical trial participation, treated by the MDTs being studied. Poor communication did not seem to be a determining factor as to whether or not patients joined a trial, but trial design, especially if one arm appeared to be offering less treatment, did seem to deter some," conclude the authors.

Trials comparing shorter durations, they add, could evoke anxiety about efficacy. "In contrast, trials that had a standard drug plus or minus a new drug appeared more attractive, perhaps because the patient would not feel they were losing out and may even gain an extra treatment," write the authors.

■ V Jenkins, V Farewell, D Farewell et al. Drivers and barriers to patient participation in RCTs. *Br J Cancer* 16 April 2013, 108:1402–07

Study quantifies risk of ischaemic heart disease from ionising radiation

■ New England Journal of Medicine

The increased risk of ischaemic heart disease caused by exposure to ionising radiation during radiotherapy for breast cancer is proportional to the mean dose to the heart, with women with pre-existing cardiac risk factors showing greater absolute increases in risk, a population-based case–control study has found. Risk, the study found, begins within a few years of exposure and continues for at least 20 years.

Radiation therapy has evolved as a critical component of treatment for women with breast cancer who have undergone breast-conservation surgery, and for those with a high risk of recurrence who have undergone mastectomy. While older radiation techniques have been associated with subsequent cardiac disease, less is known about associations with modern radiation techniques.

In the current study, Sarah Darby and colleagues, from the Clinical Trial Service Unit at the University of Oxford, UK, undertook an investigation relating the risk of ischaemic heart disease after radiotherapy to each woman's radiation dose to the heart, taking into account any cardiac risk factors that individuals had at the time of radiotherapy.

Altogether 2168 women who received external-beam radiotherapy for invasive breast cancer between 1958 and 2001 in Sweden and Denmark were followed up. Of these, 963 experienced major coronary events (defined as a diagnosis of myocardial infarction, coronary revascularisation or death from ischemic heart disease), and 1205 acted as controls who did not. Data on each woman's medical history prior to diagnosis with breast cancer, tumour characteristics and radiotherapy treatment were obtained from hospital oncology department records.

Results show that, among the case-defining major coronary events, 44% occurred less than 10 years after diagnosis of breast cancer, 33% occurred 10 to 19 years afterwards, and 23% occurred 20 or more years afterwards. Overall, the estimated mean dose of radiation to the heart was 6.6 Gy for women with tumours in the left breast, 2.0 Gy for women with tumours in the right breast, and 4.9 Gy overall. Furthermore, the rate of major coronary events increased by 7.4% for each increase of 1 Gy in the mean radiation dose delivered to the heart.

Although the overall rate ratio for a major coronary event was 6.67-fold higher for women with a history of ischemic heart disease as compared to women with no such history, the proportional increase in the rate of major coronary events per gray was similar.

"The relevance of our findings to a woman receiving radiotherapy for breast cancer today is that they make it possible to estimate her absolute risk of radiation-related ischemic heart disease. This absolute risk can be weighed against the probable absolute reduction in her risk of recurrence or death from breast cancer that would be achieved with radiotherapy," write the authors.

In an accompanying commentary, Javid Moselehi, from Harvard Medical School, Boston, Massachusetts, writes that the study underlines the need for greater collaboration between oncologists and cardiologists. "An important lesson for the oncologist may be that the time to address concerns about cardiovascular 'survivorship' is at the time of cancer diagnosis... Similarly, cardiologists need to assess prior exposure to radiation therapy as a significant cardiovascular risk factor in survivors of breast cancer."

■ S Darby, M Ewertz, P McGale et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *NEJM* 14 March 2013, 368:987–998

■ J Moselehi. The cardiovascular perils of cancer survivorship. *ibid* pp 1055–56

Noninvasive ventilation reduces dyspnoea in patients near end of life

■ Lancet Oncology

Noninvasive ventilation (NIV) is more effective than oxygen therapy for reducing dyspnoea in cancer patients nearing the end of their life, and also allows lower doses of morphine, reports a feasibility study. The study, write the authors, is to the best of their knowledge the first to assess the feasibility of NIV as a palliative measure in comparison with oxygen in terminally ill patients.

Respiratory symptoms and dyspnoea are commonly reported in patients with solid tumours, with prevalence estimated to range from 20% to 80%. There have been suggestions that NIV, a system supporting breathing without an endotracheal tube, might offer an alternative option to relieve dyspnoea. NIV works by delivering positive pressure to support inhalation and prevents complete exhalation, thereby facilitating breathing.

In the current study, Stefano Nava and

colleagues, from Azienda Ospedaliera Universitaria, Bologna, Italy, enrolled consecutive patients with solid tumours from seven centres in Italy, Spain and Taiwan. The patients, who had been admitted to hospital because of acute respiratory failure and distress, had life expectancies of less than six months and had chosen to receive palliative care only.

Between January 2008 and March 2011, 441 consecutive patients were screened for eligibility; 234 were eligible for recruitment and 200 (85%) were randomly allocated to treatment. Prior to randomisation, each patient was given a 5- to 10-minute demonstration to familiarise themselves with NIV and allow their willingness to participate to be assessed.

Results show dyspnoea decreased more rapidly in the NIV group than in the oxygen group; the Borg score decreased by an average of 0.58 in the NIV group compared to 0.23 in the oxygen group (P=0.0012). The total dose of morphine during the first 48 hours was 26.9 mg in the NIV group compared to 59.4 mg for the oxygen group (P<0.05).

Eleven of 99 patients in the NIV group stopped treatment early, compared to no patients in the oxygen group. Reasons for discontinuation included claustrophobia, suffocation, anxiety, sense of imminent death, not understanding the protocol, and requests from relatives.

In-hospital mortality was similar in the two groups. However, in patients with hypercapnia, in-hospital survival and survival six months after discharge were better in those who received NIV than those who received oxygen therapy (HR for all deaths, 0.41; 95%CI 0.21–0.80).

"One of the main concerns about the use of NIV is the supposed low acceptance rate, especially when patients are severely dyspnoeic and anxious. ...When the technique was carefully explained and patients were given a brief trial period on NIV, and when they were assured that withdrawal from NIV was possible at any time, NIV was, in general, well accepted," write the authors.

In an accompanying commentary, Anita Simonds from the Royal Brompton and Harefield NHS Foundation, London, UK, writes, "Clinical teams should set goals such as reduction in dyspnoea or symptom burdens when the aim of NIV is to palliate symptoms rather than act as life support, so that if these objectives are not achieved NIV can be rapidly withdrawn and will not add to a patient's burdens."

■ Stefano Nava, M Ferrer, A Esquinas et al. Palliative use of non-invasive ventilation in end-of-life patients with solid tumours: a randomised feasibility trial. *Lancet Oncol* March 2013, 14: 219–227

■ A Simonds. Palliating breathlessness in patients with advanced cancer. *ibid* pp 181–182

Spin plays a role in reporting of clinical trials

■ Annals of Oncology

Investigators commonly use spin to emphasize secondary results when primary endpoints are not significant, a Canadian study has reported. The analysis also revealed deficiencies in the reporting of severe toxicities.

Reviews have suggested that a substantial proportion of clinical trials have suboptimal reporting of harm, especially of severe toxicity. In the current study, Ian Tannock and colleagues, from Princess Margaret Hospital, Toronto, Canada, evaluated the quality of reporting of primary endpoints and of toxicity in randomised controlled trials for breast cancer. The investigators chose to focus on breast cancer, given that it is the most common malignancy in women, has substantial mortality and is a cancer site involving a large number of trials.

Using PUBMED, the investigators identified 164 clinical trials for breast cancer (148 for systemic therapy, 11 for radiation therapy and five for surgical therapy) published between 1995 and 2011. For inclusion, trials needed to be phase III studies, published in English, including patients aged over 18, and have sample sizes greater than 200 patients. There was a focus on trials that had the potential to change clinical practice.

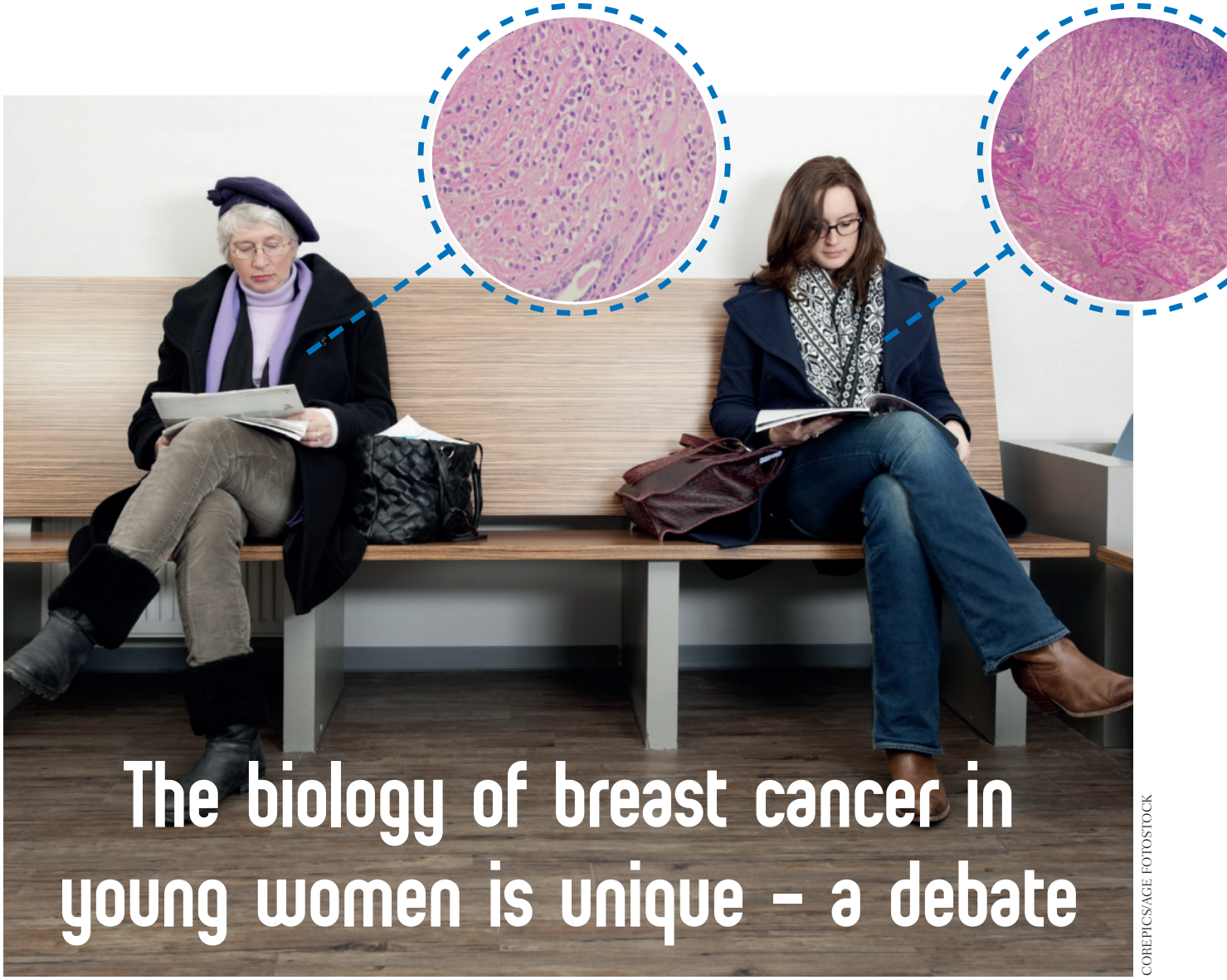
Results showed that 72 studies (43.9%) were positive, with a significant P-value for the difference in primary endpoint favouring the experimental arm, compared with 92 (56.1%) with a non-significant P-value. Of the 92 trials with a negative primary endpoint, 59% used secondary endpoints to suggest benefits for experimental therapy. Furthermore, only 32% of articles indicated the frequency of grade 3 and 4 toxicities in the study. When the investigators rated the reporting of toxicity on a hierarchical scale, ranging from 1 (excellent) to 7 (very poor), they rated 34 trials as 7, 55 as 6, and 21 as 5.

Although 67% of the trials were industry sponsored, the authors found no association between industry sponsorship and biased reporting of either efficacy or toxicity. The majority, 150 trials (91.4%), were published in medium- or high-impact journals, with the median impact factor for all the journals calculated as 19.

To avoid selection for publication of positive trials, and/or publication of a subset of the original recorded outcomes on the basis of the results, write the authors, registration of trials is now mandatory. However, ClinicalTrials.gov was only established in 2002, with just 18% of the 164 trials analysed in the study registered. "Trial registration does not necessarily remove bias in reporting outcome, although it makes it easier to detect," they add.

Bias in the reporting of efficacy and toxicity, conclude the authors, remains prevalent. "Clinicians, reviewers, journal editors and regulators should apply a critical eye to trial reports and be wary of the possibility of biased reporting. Guidelines are necessary to improve the reporting of both efficacy and toxicity," they write.

■ F Vera-Badillo, R Shapiro, A Ocana et al. Bias in reporting of end points of efficacy and toxicity in randomized, clinical trials for women with breast cancer. *Ann Oncol* May 2013, 24: 1238–44



The biology of breast cancer in young women is unique – a debate

COREPICS/AGE FOTOSTOCK

Breast cancer in young women frequently presents with an aggressive phenotype, leading to a poorer prognosis than in older women. The critical issue centres on whether the drivers of this 'poor-prognosis' phenotype in young women represent a distinct biology or reflect an over-representation of molecular and cellular processes that underpin aggressive disease in all women with this common malignancy. Addressing whether or not the biology of breast cancer in young women is truly unique is an important question, as it increases our understanding of the disease process, while informing the provision of appropriate optimal quality care for the young breast cancer patient. Here, Marco Colleoni, from the European Institute of Oncology in Milan, Italy, and Carey Anders, of the Lineberger Comprehensive Cancer, in North Carolina, USA, offer alternative viewpoints, which they originally presented in a live debate conducted during the European School of Oncology's conference on Breast Cancer in Young Women (BCY1, November 2012, Dublin, Ireland).

IN FAVOUR
Marco Colleoni

Breast cancer at a young age has been reported to pursue a more aggressive clinical course and to be associated with a poorer prognosis compared with disease in older women[1]. Factors influencing poor prognosis in this patient group include higher tumour grade at diagnosis, high tumour proliferation, pronounced vessel-invading disease, increased expression of HER2 (ErbB2) and reduced expression of both oestrogen (ER) and progesterone receptor (PR)[2].

Both immunohistochemical (IHC) and molecular classifications have been employed to address whether cancer biology defines a unique disease in young women with breast cancer[3–6]. Previous research has identified four subtypes: luminal A (less-aggressive subtype), and luminal B, HER2-enriched, and triple negative (more-aggressive subtypes), which have prognostic relevance[6,7]. Evaluation of these four subtypes in a cohort of 2970 young patients, which included a subset of 'very young women' (<35 years) with breast cancer, indicated that there were significantly more patients with triple-negative subtypes and significantly fewer luminal A subtypes in the 'very young' cohort when compared with the 'less young' women[8]. Other studies have also identified luminal subtypes in older patients[9], with triple-negative subtypes over-represented in women younger than 40 years of age[10]. The finding that 'very young' patients with tumours classified as luminal B, HER2-enriched and triple-negative subtypes were at increased risk of relapse, when compared with older patients with the same subtype[8], suggests that younger patients with breast cancer may exhibit a unique biology.

Further evidence for a unique biology in breast cancer in young women comes from molecular ➤

AGAINST
Carey Anders

There is no question that breast cancer arising in young women is unique in many aspects. Challenges faced by young women diagnosed with breast cancer are often quite different from those experienced by older women. These unique challenges may include disruption of career in its early phase, child-bearing and ongoing family responsibilities, impact of therapy on sexuality and body image, and the psychosocial toll of facing a life-threatening illness at a young age. Historically, multiple studies have shown that younger women tend to experience worse breast cancer outcomes as compared to their older counterparts[1–3]; however, the reason for this observation is not entirely understood.

Immunohistochemical (IHC) and gene expression profile studies have also shown that the more-aggressive subtypes of breast cancer (i.e. basal-like and HER2-enriched) are over-represented among younger women as compared with older women[4,5]. Analysis of 784 early-stage breast cancers, which included women aged ≤45 years (n=200) and women aged ≥65 years (n=211) identified distinct clinical-pathological features (low IHC oestrogen receptor [ER] expression, high IHC HER2 expression, larger tumours and higher tumour grade) in younger women[6]. Gene expression analysis indicated a significantly lower expression of ER and progesterone receptor mRNA and a significantly higher expression level of HER2 and epidermal growth factor receptor (EGFR) mRNA in younger women.

A more detailed view of the biology of young women's breast tumours, obtained by analysing microarray data from several large, publicly available data sets in a non-subtype-dependent manner, indicated that breast tumours arising in younger women were enriched for 367 biologically relevant gene sets ➤

The Oncologist

This article was first published in ***The Oncologist*** vol. 18, no.4, and is republished with permission. © 2013 Alpha Med Press doi:10.1634/theoncologist.2013-0118

studies. Young women with breast cancer have a significantly increased prevalence of the more-aggressive subtypes, in particular the 'basal-like' tumours[9,10]. Meta-analysis of prognostic signatures and gene classifiers from 20 data sets, representing over 3500 patients aged ≤40 years, indicated that distinct molecular processes, including those related to immature mammary epithelial cells and growth factor signalling, are over-represented in breast cancer arising at a young age[11]. Particular genes/processes that were enriched included RANKL, c-Kit, BRCA1-mutated phenotype, mammary stem cells, luminal progenitor cells (immature mammary epithelial cell phenotype), mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)-related pathways (growth factor signalling phenotype). A prognostic effect of stromal-related gene signatures was also observed, suggesting a role for the microenvironment in mediating breast cancer growth and proliferation in young women, leading to a more-aggressive phenotype.

Thus, both IHC-defined subtype and molecular classification data indicate that breast cancer that develops at a young age is different biologically from that arising in older premenopausal and postmenopausal women.

when compared with older women[6], suggesting, with the IHC data, a unique biology for breast cancer in younger women. Independent analysis of a second pooled data set, which included women aged ≤45years and women aged ≥65 years confirmed the increased incidence of the more-aggressive basal-like and HER2-enriched subtypes in younger women[7]. However, when correcting for significant clinical-pathological and histopathological features, including grade, nodal status, ER status and intrinsic breast cancer subtype, adjusted models yielded negligible gene differences between breast tumours arising from defined age groups of ≤45 versus ≥65 years[6,7]. As is standard in the field, this finding was replicated in an independent data set as part of this analysis, further confirming these results.

Based on these results, age alone does not appear to offer an additional layer of biological complexity above that of breast cancer subtype and grade. These data support the argument that the biology of young women's breast tumours may not be unique, but rather an over-representation of aggressive, biologically driven subtypes is accounting for the disparities observed in outcome by age.

While the information generated by gene expression profiling is compelling, many unanswered questions remain, including: (1) why are younger women more prone to aggressive subtypes of breast cancer? (2) what is the role of the microenvironment? (3) how does breast density and/or other factors (e.g. breastfeeding, parity) contribute to these findings? and (4) will disparities in outcome persist in the era of modern targeted therapies? – all areas deserving of further research.

Overall conclusion

The question as to whether younger patients with breast cancer exhibit a unique biology is a controversial one. All of the data presented both in favour of and against this hypothesis indicate an increased incidence of more-aggressive molecular subtypes in young women with breast cancer. It may be that factors such as the cut-off age for younger patients need to be considered – perhaps a different biology underpinned by basal-like or HER2-enriched molecular subtypes is implicated in very young patients (i.e. younger than 35 years of age). A precise consideration of the role of the stromal microenvironment may also be relevant and should be pursued. In any case, it is clear that our increased understanding of breast cancer tumour biology in younger women is starting to inform a new scientific rationale (e.g. targeting of genes like RANKL or growth factor pathways like PI3K), that may be of particular benefit to this poor-prognosis cohort of patients. ■

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

My World

Mariagrazia De Lisa is a second-year resident at the medical oncology department of the university hospital Ospedali Riuniti delle Marche, in Ancona, Italy. She came top out of 63 other students from 25 countries in the learning assessment test at the end of this year's ESO Masterclass in Clinical Oncology.

Why I chose to work in oncology

Oncology is the medical branch that offered me the greatest opportunity to combine clinical activity with biologic studies. It also meant a lot to me because someone very close to me suffered from cancer.

What I love most about my job

I like the fact that I take care of the person/patient as a whole: the medical aspects, but also psychological and family ones. I also love the opportunity it gives me to build and maintain strong relationships with patients and their families, sharing with them hopes and difficulties, successes and failures.

The hardest thing about my job

Despite sharing very deep feelings with patients and their relatives, I am all the time required to keep my professional attitude. The need to coordinate well with several other medical figures working with the patient adds interest to the job, but is also a challenge.

What I've learned about myself

Working in oncology has taught me to value the presence of my parents and people I love the most, because you never know what could happen in the future. I appreciate more the simple things of life that I used to take for granted – being able to work, study, walk and live an autonomous life.

I'll never forget

All the professors and colleagues who have set an example and transmitted to me the passion required to do this work. I remember one in particular, who a group of us accompanied in a visit to a young patient with a colorectal cancer. After asking about his familial history, he started to focus on his face and body skin, looking for spots around and inside his mouth and nostrils. He then asked us which syndrome he was suspected to have. This taught me about the process of clinical reasoning.

A high point in my career

I'm just starting out, and at the moment I am very happy just to be working next to very skilled and highly qualified people. I hope to have the opportunity to get experience abroad.

I wish I were better at ...

Speaking in public. I would like to improve my self-confidence and the capacity to promote my own ideas, opinions and projects.

What I value most in a colleague

Sincerity and the capacity to collaborate and work in team to guarantee the best care for the patient.

The most significant advance in my specialism in recent years

Learning more information in more depth about the biomolecular pathways that control the growth and cell proliferation at the base of carcinogenesis I believe has been the most important, interesting and exciting progress in oncology.

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

Sincere passion and a true commitment are both required to work in a field where disappointments and failures happen quite frequently. Your relationship with the patient and their family is the biggest source of satisfaction.

What I wish I'd learnt at medical school

I'd like to have gained more confidence in applying the evidence-based medicine approach, in order to have a better grounding in how to deal with clinical studies and the world of scientific research. ■