



March-April 2015

Number 65

cancerworld

ANTIBODY-DRUG CONJUGATES

More toxic, better targeted – are we one step closer to that magic bullet?

YOU MAY FEEL A LITTLE TIRED

The dangerous gap between perceptions and the reality of side effects of targeted drugs

BENEFITING FROM GENERICS

What governments and clinicians must do to protect quality of care

Francesco Pignatti

Walking the line between quick access and evidence





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HarrisDPI
www.harrisdpi.com

Printed by

A4 Servizi Grafici di Serra Sergio & C. s.n.c.

Cover photograph

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Published by

European School of Oncology

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Registrazione Tribunale di Roma
Decreto n. 436 del 8.11.2004

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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





Better outcomes data lead to better outcomes

RICCARDO AUDISIO GUEST EDITOR

The right treatment, for the right person, at the right time' represents a significant shift from 'one-size-fits-all' medicine to a tailor-made individualised approach. While we are learning fast about how individual tumour characteristics affect each patient as a unique host, what we lack are validated tools to identify who benefits from which treatments.

We need to greatly improve our ability to monitor the impact of treatments on outcomes. Cancer registration and quality assurance programmes are key; the challenge lies in identifying the right quality indicators, which need to be robust and feasible to monitor across many countries. EU member states use different ways to collect cancer data, and even different versions of the TNM classification, making it difficult to compare like with like. The last couple of years, however, have seen important progress in defining minimal datasets for several tumour types, which have been shared across different international registries.

Randomised clinical trials (RCTs) are another important source of evidence, but their ability to inform a personalised approach to the care of patients in the real world is strictly limited. Less than 1% of all cancer patients are treated inside a clinical trial, and they tend to be younger and fitter than the average patient and with fewer comorbidities.

Publication bias is also a matter of concern. If the results of trials with negative outcomes are kept in the dark, clinical guidelines will be skewed in favour of the positive trial findings –

the bias can be magnified in meta-analyses.

Large observational population-based registries, with complete and accurate information, provide much more robust and detailed information than RCTs on how different aspects of patient management impact on outcomes in different patients. Ideally, population-based research should be designed as a comparison between different geographical areas, each one using different treatment approaches. This type of research is becoming easier as our ability to collect good-quality data in 'real time' is improving.

The value of geographical comparisons has recently been shown, for instance, in the field of rectal cancer, where data showed that patients in the Netherlands were more likely to receive preoperative radiotherapy than their counterparts in other European countries but, despite lower rates of recurrence, they were not living longer as a consequence.

EURECCA, the European Registration of Cancer Care (www.canceraudit.eu), is a good example of an international multidisciplinary platform set up to gather these types of data to raise standards of cancer care across the board.

It is clear that RCTs continue to provide important data upon which we base our practice; however, the time has now come to move beyond this, and to invest in population-based registries such as EURECCA.

A better future requires international cancer registration. All cancer registries and regional/national clinical audits need to work together to make it happen! ■

Riccardo Audisio is a consultant surgical oncologist at St Helen's Teaching Hospital in Liverpool, UK, and President of the European Society of Surgical Oncology (ESSO) and of the British Association of Surgical Oncology (BASO)

Francesco Pignatti

Walking the line between quick access and evidence

SIMON CROMPTON

How do you decide which new cancer drugs to approve, when statistical certainty takes too long to wait for and essential evidence on quality of life is hard to measure? The head of the cancer section at the European Medicines Agency is keen to explain his approach.



JASON HARRIS

Once upon a time, way back in the 20th century, regulating cancer drugs was a simple affair. When the European Medicines Agency (EMA) was founded in 1995, it had to balance the relative risks and benefits of one or two broad-reaching chemotherapy agents which had shown signs of activity on a wide section of the population, and then make a ruling on whether they were safe and effective enough to be marketed.

How quickly things changed. At the turn of the century, the arrival of monoclonal antibodies such as rituximab and trastuzumab marked the beginnings of a transformation not only of cancer therapies but the challenges facing those who regulated them.

A cascade of new targeted drugs that delivered high response rates in specific indications brought with them new demands for speedy access from patient groups. Ever since, the EMA has been trying to find effective ways to balance the public and professional demand to make these new drugs available with an authoritative assessment of their efficacy and safety.

Based in an airy glass tower in London's Canary Wharf, alongside prestige companies such as Barclays Bank and the State Street Corporation, the EMA's 800 staff, seven scientific committees and numerous working parties are responsible for the scientific evaluation and market authorisation of medicines for use throughout the European Union.

In charge of its cancer drug evaluation is Francesco Pignatti, an Italian medical doctor who arrived at the EMA from the European Organisation for the Research and Treatment of Cancer (EORTC) 15 years ago.

As he answers my questions thoughtfully from the 4th floor of the EMA block, gazing out at a grey London view, he identifies the challenge regulators face when considering whether the drugs presented to them by pharmaceutical companies merit market authorisation.

"Our dilemma is how to deal with the uncertainty that inevitably surrounds evidence while at the same time trying to meet the needs of patients who are in desperate need," says Pignatti, whose formal position is Head of Oncology, Haematology and Diagnostics in the EMA's Human Medicines Evaluation Division. "It's not easy, because different stakeholders have different views."

Pignatti is serious, careful in his words, but also seemingly determined not to sidestep difficult issues. During the course of our interview, he portrays an agency acutely aware that it has to be honest about the fact that balancing risk and benefit is a matter of fine judgement that leaves it constantly open to criticism. He presents an organisation looking to be innovative as it attempts to make justifiable judgements within the realms of scientific uncertainty, while the needs and demands of patients press ever harder.

Drugs regulation, he says, is changing to pay heed to research beyond randomised controlled trials and embrace the opinions and experiences of patients far more than in the past.

Today's regulators can no longer wash their hands of difficult decisions about availability and affordability of cancer drugs – decisions that loom large in national media and consciousness. Though it is for payers and health technology assessment (HTA) organisations, not the EMA, to decide how widely a drug should be made available in each country, Pignatti believes that the new world of varied and expensive cancer drugs requires regulators to work with payers and health technology assessors to convey clear messages about the kind of data needed to prove a drug's worth.

And he is at pains to dispel the myths about regulators: that they are not interested in quality of life research when assessing drugs, or that they expect the same standard of evidence for rare cancers as common cancers. Such misconceptions are standing in the way of good drug development, he tells me.

But it is the word "uncertainty" that recurs throughout our interview and provides its theme. To explain the challenges that the EMA faces, Pignatti recalls that one of the first drugs that the EMA approved was Taxotere (docetaxel) for breast cancer in 1995 – it did so under the European legal provision of "exceptional circumstances" for drugs which had not yet completed trials, or where trials were small, but there were indications of a very high response rate.

"As a regulator you have a choice. You can wait another five years, do a big trial where you show differences in survival, or you can say I am convinced by the evidence which I have today despite the uncertainty, because the drug will fulfil an unmet need. This is actually quite characteristic

of most cancer drug approvals. Almost half of them have been approved based on a response rate or an endpoint which comes with a big uncertainty.” This is known as conditional approval.

“Endpoints” are a subject close to Pignatti’s heart. He has discussed them extensively at international oncology conferences and written about them in a range of journals. A research fellow at the EORTC Data Centre, Brussels, from 1995, he was involved in clinical trial design, conduct, analysis, and reporting, and then from 1997 was Medical Advisor for the Gastrointestinal Tract Cancer Cooperative Group and Brain Tumor Cooperative Group.

“Conditional approvals arise typically when you are approving based on a surrogate endpoint. Obviously, when researching a drug, a true endpoint would be mortality – you find out whether a drug affects death. But if you don’t have time for that you use a surrogate which you believe to be correlated with a true endpoint, for example tumour shrinkage.”

So soon after conditional approval became embedded in European law in 2006, the renal cancer drug Sutent (sunitinib) was approved on the basis of a high response rate in two trials, and after that a stream of other cancer drugs were authorised on a similar basis. “The legislation has adapted to deal with the uncertainty that we are used to having in oncology,” says Pignatti. “And as large indications fragment into many well-defined subsets, the situation is likely to continue.”

The EMA has developed the concept further. In March 2014 it invited pharmaceutical companies to participate in a project piloting adaptive licensing, also known as adaptive pathways, staggered approval or progressive licensing. This starts with the early authorisation of a medicine in a restricted patient population, followed by phases of evidence gathering and marketing authorisation adaptation to allow broader patient populations access to the medicine. It is particularly relevant for drugs with the potential to treat serious conditions where there is an unmet need.

“No longer is regulation all about the magic moment when your drug gets on the market. It’s trying to be as rational as possible about when you have enough evidence, maybe in a small population with some uncertainty – but you can still say the benefits outweigh the risks and put it on the market for a limited group. Then you have a clear



A team effort. Pignatti with the staff of the Office of Oncology, Haematology and Diagnostics in EMA’s Human Medicines Evaluation Division

plan for how to fill the uncertainty gap with data post-marketing.”

So how do you fill the uncertainty gap after marketing has started? Once a drug hits the market early, say through adaptive licensing, you can no longer complete a randomised clinical trial on the same indication because ‘equipoise’ – true uncertainty about which trial arm will benefit patients – has been lost.

This, says Pignatti, is a challenge. “We are having to look seriously into new methods. For example, observational studies have been used to assess safety for years and now the challenge is to use this type of evidence for efficacy. There are many confounders and so on, but I think it’s the beginning.”

Does he not worry that once a drug has been authorised early, the momentum for companies



JASON HARRIS

spread use. Trials in related indications or different populations may provide enough evidence to satisfy regulators, but it may not be enough for payers.

Pignatti hopes that such dilemmas will be eased by a new awareness of the need for collaboration between all the stakeholders in drug development. In 2010 the EMA launched a pilot project enabling drug developers to get joint feedback from the EMA and health technology assessment bodies (such as the EUnetHTA) about the kinds of evidence they will require for market authorisation and widespread availability. “There’s a clear opportunity to design the development in such a way that all stakeholders maximise the chances of fulfilling their objectives as quickly and rationally as possible,” he says.

He stresses that this in no way implies that the processes of regulation and HTA are being pushed together – by law, the EMA has to exclude economic considerations from its decisions. “But we can discuss evidence standards with HTAs. There’s often a lot of convergence, and even if there isn’t you can find a rational way to ensure that each stakeholder fulfils their objective. For example, a trial may deliver a certain endpoint at a certain time, but then we will continue to follow patients to observe a second endpoint which may be of interest to other stakeholders.”

Patient involvement is also becoming more integral to EMA’s decision-making – though Pignatti acknowledges it has developed gradually. He says the agency is becoming more and more aware of patients’ unique expertise and their ability to inform research assessment about what really matters to real

people – quality of life factors, for example.

Since 2005, the EMA has had a Patients’ and Consumers’ Working Group providing recommendations on matters of interest to patients in relation to medicines, and there are patient representatives for instance on the orphan drug committee.

The EMA committee that makes final decisions about drug authorisations – the Committee for Medicinal Products for Human Use (CHMP) – does not include a patient representative, but brings in scientific advisory groups of clinicians, statisticians and patients whenever the benefit-risk equation stands on a knife-edge, or there is



to follow up with authoritative, gap-filling research will be lost? The long-term effectiveness of many targeted therapies are still unknown, and there are increasing indications of acquired resistance which will surely need to be understood better.

Pignatti nods. He argues that there is a huge incentive on industry to carry on researching their products because payers are only likely to reimburse expensive products if the evidence of meaningful benefit is strong. All the same, the problem remains of how to produce that evidence once a drug has been approved early, trial participants have switched treatments and the drug is in wide-

a disagreement on the committee. It is in this sphere that patient viewpoints are becoming more and more influential, explains Pignatti.

“Benefit–risk assessment often isn’t just about very precise quantities or statistical significance or *P* values,” he says. “There is almost always a very important subjective component. You have to use value judgements to compare two, three or four benefits to multiple risks. In the past, this exercise has been done implicitly at committee level – but it makes it less accountable.

“So we’re trying to be more transparent about why we think certain benefits outweigh the risks, or vice versa. Recently we’ve had many discussions of this kind with patients via our scientific advisory groups, and it’s often the case that they may be more concerned about quality of life than we thought they would be. There has been a lot of scepticism over the years about using quality of life measures in oncology, because the data aren’t very robust. But we are now developing a new guideline saying that quality of life measures may be imperfect, but they do tell us something about what patients think. We cannot dismiss them.

“Maybe regulators have to do more to encourage the collection of good data on quality of life rather than dismissing it as an endpoint. It can be very important for health technology assessments too.”

Patient input has been especially important in forging a way forward on rarer cancers. Last October the EMA hosted a meeting with representatives of Rare Cancers Europe to discuss RCE’s consensus paper on the methodology of clinical trials in rare cancers. Afterwards, the EMA made clear its willingness to examine evidence sources beyond randomised clinical trials – since large trials are clearly not possible for conditions that affect a small number of people.

“I hope that as a result of this meeting we will be able to plan at least two or three more meetings to figure out the problems in specific disease areas and how regulators can help. There is a lot of misconception about regulatory requirements in rare diseases, and this puts companies off invest-

ing. They believe they can never achieve the evidence standard that regulators require, but in fact we have had situations in the past where all we have had to show that a drug was safe and effective was a series of case studies.”

Equally, people wrongly assume that regulators aren’t interested in patient-reported outcomes, says Pignatti. “We will not dismiss them. However, these data are currently often poor. So the message now is: improve the quality of patient-reported data collection. There are a number of good quality of life tools, and the data collection can be done much better now using electronic means, for example using daily phone reminders prompting patients to enter information.”

Regulators need to be more open about the fact that value judgements play a part in their decisions, says Pignatti. “At the end of the day, you



have to make a decision, whether your data are robust or not. It will increase our transparency if we can say: ‘These are our value judgements, we have consulted with patients, these are their value judgements, this is the thinking that has led to our decision.’ We have never tried this, but I hope we will be able to.”

The EMA took a major step towards greater

“Quality of life measures may be imperfect, but they do tell us something about what patients think”

transparency with the announcement last October that, from January 2015, it would disclose all the trial data that has informed its decisions. Third parties will be allowed access to clinical data to verify the original analysis and conclusions, “to examine the regulatory authority’s positions and challenge them where appropriate,” states the policy.

The EMA is the first regulatory body in the world to introduce such rules, and the move has been welcomed by the founder of the All Trials campaign for greater scientific openness, Carl Heneghan, as “a real shift in favour of ensuring research data is shared routinely and re-used effectively in the public interest.”

However, the response hasn’t been universally positive. When the EMA proposed the changes in 2012, freedom of information campaigners said the EMA was lagging behind forward-thinking pharmaceutical companies, while industry expressed grave concerns that the change threatened the business value of its investments because it would reveal “commercially confidential” information. In the final proposals, the EMA allows companies to black out commercially confidential information, but now campaigners for the free availability of pharmaceutical data say this leaves the way open for wholesale censorship.

Pignatti insists that any deletions will be restricted to information about commercial aspects, such as manufacturing methods, which have no general scientific interest. “The motivation behind this new policy is to avoid duplication of research, to provide data to the community which might be useful, to find prognostic factors for future trials and so on.”

“We’re already quite transparent about the decisions we have made, publishing reports, often hundreds of pages long, describing the data we have examined. This goes one step further, allowing secondary analysis of the data by researchers who want to use them for further research or to scrutinise our decisions.”

The EMA has also been in the firing line about how long its drug authorisation process takes. A review published in the *British Journal of Clinical Pharmacology* in 2013 found that approval times for tyrosine kinase inhibitors (TKIs, such as Glivec/ imatinib) were on average twice as long as in the US – 410 days as opposed to 205. How does Pignatti feel about that, when patients are crying out for the new treatments?



JASON HARRIS

“I very much understand the expectation of patients when they are in that situation and I think we have to do our absolute best to meet those expectations,” he says. “I think the FDA has been very effective in reducing the review time for a number of cancer drugs. We also have provisions in legislation that allow us to accelerate an assessment of drugs that represent major therapeutic innovations, but these have been used only rarely.” One example of fast approval was for Glivec for chronic myeloid leukaemia in 2001. “It is difficult for me to comment on why the CHMP has not decided to avail itself of these mechanisms more frequently.”

But when people compare the speed of the EMA

“Regulators need to be more open about the fact that value judgements play a part in their decisions”

review times with those of the FDA, they are perhaps concentrating on the wrong thing, says Pignatti.

“Maybe we should look instead at the speed of the whole development. What are the mechanisms to bring effective drugs to patients before approval?” Pignatti says that pharmaceutical companies should find efficient ways beyond clinical trials for people to access drugs that have been heavily hyped in the media. It is wrong, he says, that often the only access route to a promising new agent in the absence of any valid alternatives is through randomised clinical trials, where a patient might find themselves on the non-active arm. When equipoise is lost, drug companies could provide access to at least some patients and investigators through observational studies, which, in addition, can still provide meaningful data.

“If pharmaceutical companies are afraid to open up a compassionate use programme because they are worried about losing the patient population for their trials this is the wrong approach.” Pignatti apologises for soundings defensive on the subject.

Comparisons with decisions and timing by other regulatory bodies around the world have also led to criticism. A number of papers in oncology journals have pointed out that, despite the submission of identical supporting data from clinical trials, the EMA and FDA have come to subtly different findings which are not obviously explainable.

In 2011 the *Journal of Clinical Oncology* published research showing that of the 100 indications for 42 cancer drugs evaluated by the EMA and FDA between 1995 and 2008, 19 indications were not approved by one or other of the agencies and 10 had different label wording with significant clinical meaning. For example, in 2011 the FDA withdrew an authorisation for using Avastin (bevacizumab) for advanced breast cancer following new data, while the EMA kept its use in combination with chemotherapy.

But Pignatti points out that these decisions are not made randomly or in isolation. What people might not know is that the EMA is constantly col-

laborating and comparing notes with the FDA, and other regulatory authorities in Canada, Japan and elsewhere, through monthly teleconferences.

“We go through the products we are assessing, and though we don’t try to achieve common decisions it’s very important that we don’t think in isolation. Drug development is on a global scale so regulation has to be aware on a global scale. Our processes and the efficiency of our processes may be different, but I think it’s very important that on methodological issues we achieve good alignment.”

“If there is a divergence, it will often have been discussed with our colleagues before we make a decision. If we think there is a justifiable reason why we should do differently than another regulator, then we make every effort for this to be understood. As I said, you are dealing with a lot of uncertainty here, and balancing benefit and risk there can be a narrow line between going one way or another.”

And so we come back to uncertainty. It is 20 years since the EMA was set up, and Pignatti believes that moving forward on cancer drugs over the next 20 must involve acknowledging and embracing methods to deal with uncertainty – for all the challenges that creates. It is, he says, always worth keeping in mind the end goal.

“Obviously there is a very high responsibility and no one person can take this on, which is why we have experts and committees and work in a very European-style bureaucratic system. But it works. If all the legal requirements are met in terms of safety and efficacy, and a drug receives a marketing authorisation, you see the end stage of all the successful drug developments for people with cancer. It is a very nice place to be.” ■



More toxic, better targeted: are we one step closer to that magic bullet?

RACHEL BRAZIL

Could the new generation of antibody–drug conjugates herald a move away from conventional untargeted chemotherapy? Much will depend on how far – and in whom – their added benefit can justify the high cost of these technologically sophisticated drugs.

After an apparent lull in progress of more than a decade, in the last two years, two antibody–drug conjugates (ADCs) have been approved. ADCs combine an antibody designed to target cancer cells, with a linker molecule connected to a highly potent cell killing toxin. They can therefore deliver anticancer agents directly to tumour cells, limiting the exposure of healthy tissue to the toxic drug, with the view to providing more successful treatments with fewer side effects.

Today, around 70 ADC clinical trials are underway for cancers including the lymphomas, breast, colorectal, kidney and lung. So does this current renaissance in ADCs finally herald the arrival of a new

generation of highly effective but less toxic cancer treatments?

The development of ADCs has not been without false starts. The idea dates back to 1897 when German Nobel laureate and founder of chemotherapy, Paul Ehrlich, noted “antibodies are in a way magic bullets that identify their target themselves without harming the organism.” He envisioned that, by attaching toxins to them, such a therapy could selectively kill microbes or cancer cells. The first ADC to receive regulatory approval was 15 years ago. Mylotarg (gemtuzumab ozogamicin) received accelerated approval in the US for use in patients aged over 60 with relapsed acute myelogenous leukaemia. But in 2010, Pfizer withdrew the

drug from the US market after a follow-up trial showed no improvement in clinical benefit and a greater number of deaths in those who received it, compared to those receiving chemotherapy alone.

Although there are ongoing European trials using a lower dosage, Mylotarg’s initial failure illustrates some of the fundamental problems with the first generation of ADCs. ADC drug payloads are more toxic than most conventional chemotherapy drugs, so if targeting is not accurate, there is the potential for more, rather than less, damage to healthy cells. With Mylotarg, the suggestion was that its target, the cell-surface protein CD33, was not as selective for tumour cells as first thought, and there were also



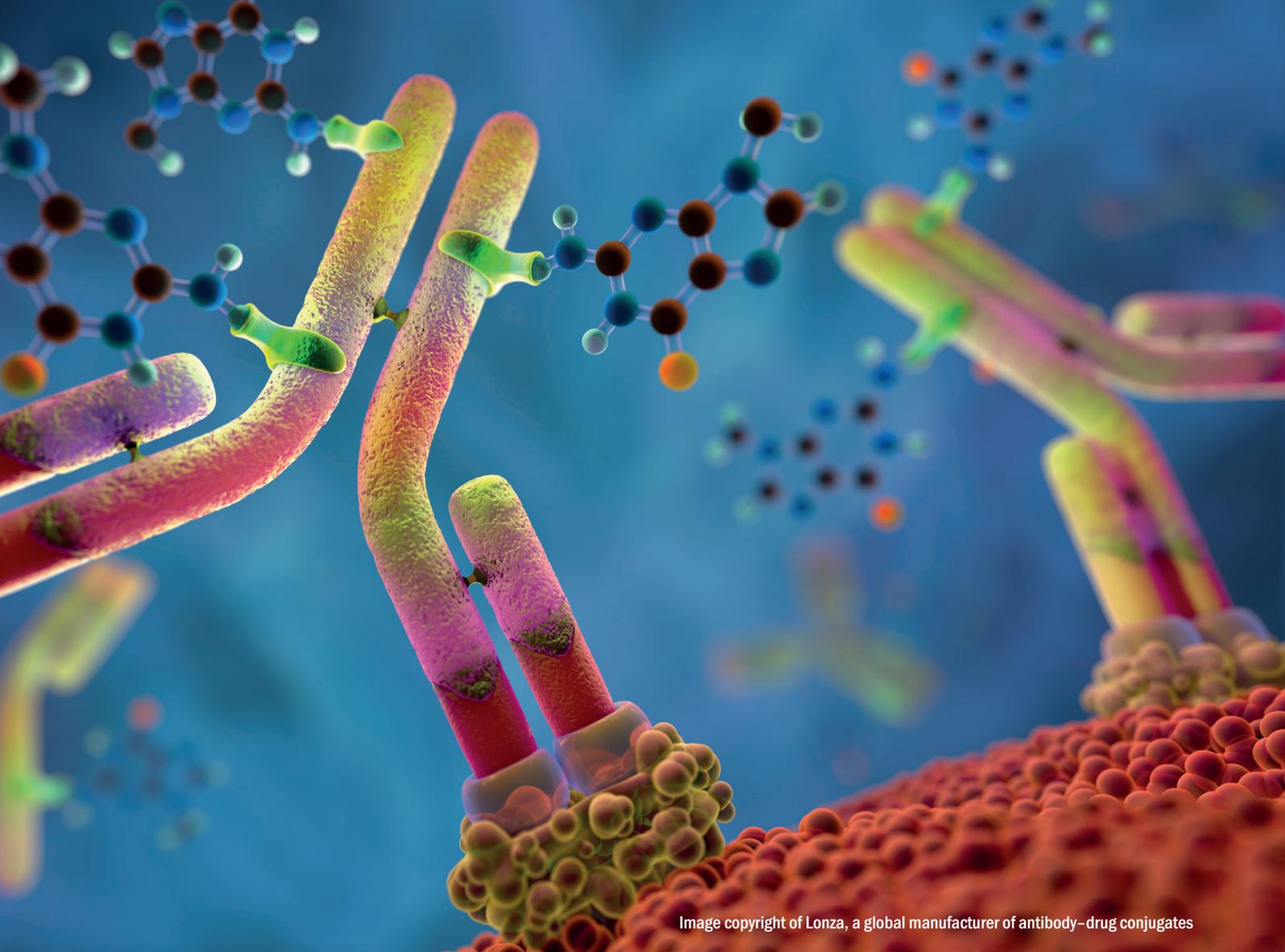


Image copyright of Lonza, a global manufacturer of antibody–drug conjugates

problems with early breakage of the linker between the antibody and drug, allowing the toxic payload to be released before reaching its target.

No other ADCs made it to market between 2000 and 2011, but after 10 years of further research a second generation of ADCs is now emerging. The first of the two currently licensed ADCs is Seattle Genetics' Adcetris (brentuximab vedotin), approved in 2011 in the US and 2012 in Europe for relapsed Hodgkin lymphoma and relapsed anaplastic large cell lymphoma. Composed of the antibody brentuximab linked to the cancer toxin monomethyl auristatin E (MMAE or vedotin, when conjugated), it targets the cell surface antigen CD30. The second, Roche's Kadcyla (trastuzumab emtansine),

was approved in the US and Europe in 2013 for advanced HER2-positive breast cancer. It uniquely combines two active components: the HER2 targeting antibody Herceptin (trastuzumab) and the toxin mertansine. Kadcyla can add six months to the survival of patients with metastatic breast cancer (*NEJM* 2012 367:1783–91), whilst Adcetris is showing convincing patient survival data (Abstracts 3689, 3701, ASH 2012).

Ironing out the glitches

Early ADCs needed improvement in all areas including the antibody. David Thurston, Professor of Drug Discovery at Kings College London, explains that in the late 1980s, the first ADCs used mouse antibodies,

but they didn't work well because, "patients reacted significantly to the mouse antibody and the body got rid of them through excretion as quickly as possible." Then came the creation of hybrid mouse–human antibodies and, finally, fully human monoclonal antibodies, produced using immune cells cloned from transgenic mice.

For successful ADCs the antibody target needs to be unique to cancer cells to avoid targeting healthy cells, and the level of expression needs to be high, at least 100,000 per cell to ensure cell death. The ideal antigen is internalised into the cell, along with the ADC. So far, the ideal antigen expression has been found more often in haematological cancers, but ADCs are presently in the pipeline

“A good few patients were salvaged through to being transplanted – that is where the excitement is coming from”

for at least 24 different antigen targets in a variety of cancers.

According to Thurstan, it is the toxic small-molecule drug payload that is the trickiest part of an ADC to get right. “You have got to deliver a drug that will kill the tumour cells effectively, so all the payloads that have been used so far – and there aren’t many – are all highly cytotoxic,” he says. The agents used can be over 100 times more potent than traditional chemotherapy drugs because, even with their high selectivity, only a small percentage can be expected to reach the tumour – one estimate is around 1.5% of the administered dose (*Clin Cancer Res* 2011, 17:6389–97).

Improvements to the stability and versatility of linkers is also a major advance. The first ADCs were created by directly connecting the toxin molecule to the antibody using a coupling agent, but this did not provide enough stability. Current technologies use a linker molecule, usually a simple peptide, connected most frequently via antibody amino acids. “In most cases the whole complex of the antibody, linker and payload is internalised,” says Thurstan. “It goes inside the cell and then proteases just chew up the simple peptidic linker and release the drug.”

Another issue with early ADCs was the lack of uniformity in the number of attached drug molecules. Too few, and the ADC does not carry a large enough dose, too many and the conjugate becomes unstable, and may block the antibody binding site or

reduce the conjugate’s half-life in circulation, so reducing target exposure time. The goal is to produce homogeneous conjugates, in most cases with three or four drug molecules per antibody. A solution to uniform drug loading is site-specific conjugation. Two of the major forces in ADC technology, Seattle Genetics and Genentech, have developed platforms that do this. They have engineered antibodies with substituted cysteines that are able to conjugate drugs in specific positions.

Second-generation ADCs

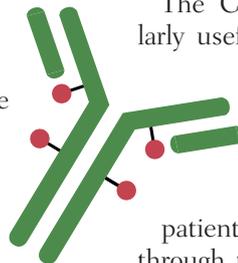
The renewed potential of ADCs is well illustrated from the results achieved with Adcetris. Adam Gibb, Clinical Research Fellow at the Christie Hospital in Manchester, UK, was part of the team carrying out the first trials outside the US in 2010–2011. Their study hit the media spotlight last year with the story of 47-year-old Ian Brooks, who received Adcetris after suffering a relapse of anaplastic large cell lymphoma.

Gibb describes the treatment as “spectacularly successful”, and says “it chewed through the disease in a matter of days” and the patient was in complete remission in 12 weeks. The EMA granted the drug conditional approval on the basis of evidence from this multicentre phase II open clinical trial. Brooks was one of 58 patients with relapsed anaplastic large cell lymphoma participating in the study, more than half of whom

(57%) achieved complete remission, with a median duration of 13.2 months (*JCO* 2012, 30:2190–96). Among 102 patients who were treated with the drug for relapsed or refractory Hodgkin lymphoma, one-third (34%) achieved complete remission, with a median duration of response for those in remission of 20.5 months (*JCO* 2012, 30:2183–89).

The Christie trial proved particularly useful as a bridge to stem cell transplants by providing patients who had already undergone multiple relapses with high-quality remission. “A good few patients were satisfactorily salvaged through to being transplanted – that is really where the excitement with brentuximab is coming from,” says Gibb. As a single agent brentuximab vedotin is still described as ‘palliative’, rather than ‘curative’, but Gibb says that from the first Hodgkin lymphoma phase II trial, which took place in 2009–2010, 10–15% of patients are still alive. The drug is in ongoing trials for a wider range of uses, including two randomised phase III trials assessing brentuximab vedotin as a first line therapy in Hodgkin lymphoma and mature T-cell lymphomas which express the CD30 antigen that brentuximab targets.

Brentuximab vedotin also illustrates the advantages of reduced side effects the ADCs can offer. It is by no means free from adverse effects, which include fatigue, nausea, infection and critically neuropathy, which Gibb says is the side effect that



caused many of his patients to “throw in the towel” after an average of 11 of a possible 16 cycles. It is, however, “a much better tolerated agent than the type of chemotherapy it is contrasted against in these settings,” he says. The off-target effects occur due to ‘bystander’ effects to nearby cells, but any healthy cells that express the antigen targeted by the ADCs are vulnerable. The CD30 antigen targeted by brentuximab vedotin is also expressed on activated lymphocytes. The washout from the dead tumour cells also presents a significant source of toxicity. But, in general, the

targeted approach of the present generation of ADCs certainly promises a significantly gentler form of chemotherapy for the future.

Beyond the blood cancers

Of the ADCs currently in clinical trials, a higher proportion tackle haematological than solid cancers. This is largely because they typically express homogeneous and more unique antigens, making them easier to accurately target. But there can also be problems getting ADCs to penetrate into solid tumours. Biotechnology company Mersana Therapeutics is

now developing a conjugation technology that could provide an answer to tackling harder-to-reach solid tumours. The company was spun out of Massachusetts General Hospital ten years ago to develop a biodegradable, well-tolerated polymer it calls ‘fleximer’. Their technology allows an increase in the ADCs’ toxic payload by linking many more drug molecules to the soluble, polyvalent polymer backbone, which is then attached to the antibody. Mersana CSO Timothy Lowinger explains “...we can take molecules of the auristatin class and we can attach 20 of them and still



ANTIBODY-DRUG CONJUGATES CURRENTLY APPROVED OR IN PHASE III OR II CLINICAL TRIALS

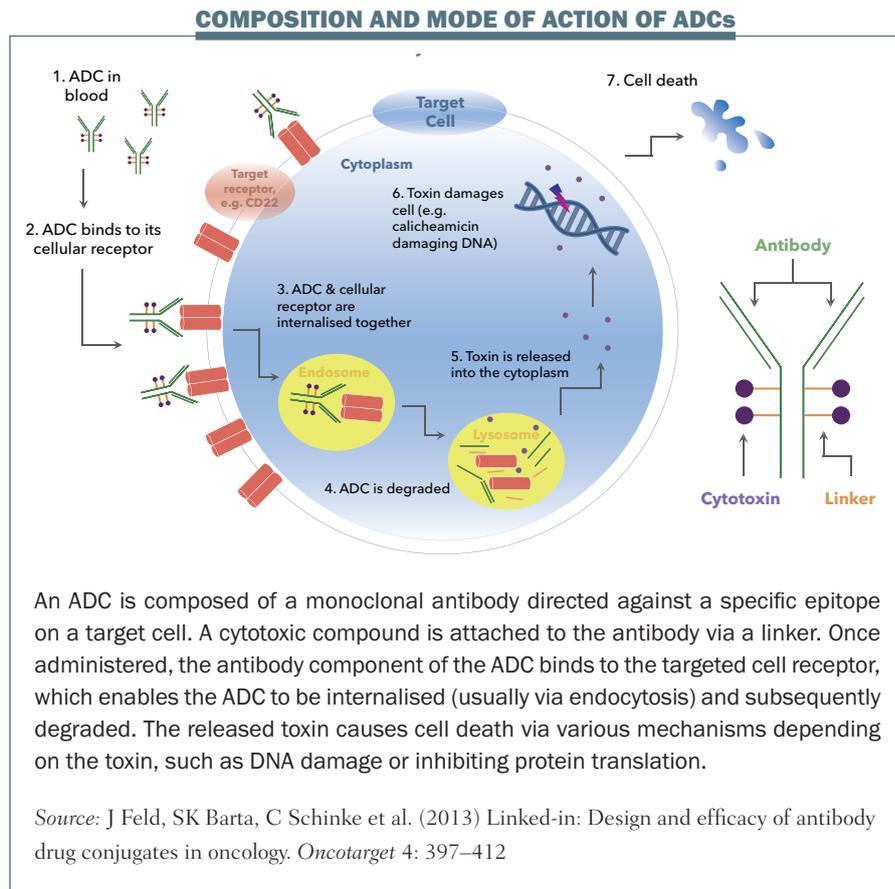
CANDIDATE	DRUG	ANTIGEN	LEAD INDICATION	DEVELOPER/PARTNER
FDA AND EMA APPROVED				
ado-trastuzumab emtansine (Kadcyla)	DM1	HER2	Breast cancer	Roche/Genentech/ ImmunoGen
Brentuximab vedotin (Adcetris)	MMAE CD30	HL/ALCL	Hodgkin lymphoma, Anaplastic large cell lymphoma	Seattle Genetics
PHASE III				
Inotuzumab ozogamicin (CMC-544)	Calicheamicin	CD22	Acute lymphoblastic leukaemia	Pfizer
Gemtuzumab ozogamicin (CMA-676)	Calicheamicin	CD33	Acute lymphoblastic leukaemia	Pfizer
PHASE II				
SAR3419	DM4	CD19	B-cell malignancies	Sanofi/ImmunoGen
RG7593	MMAE	CD22	B-cell malignancies	Roche/Genentech/ Seattle Genetics
RG7596	MMAE	CD79b	B-cell malignancies	Roche/Genentech/ Seattle Genetics
Glembatumab vedotin (CDX-011)	MMAE	GPMB	Breast cancer, Melanoma	CellDex Therapeutics/ Seattle Genetics
PSMA-ADC	MMAE	PSMA	Prostate cancer	Progenics Pharma/ Seattle Genetics

Source: RVJ Chari, ML Miller and WC Widdison (2014) *Angew Chem Int Ed* 53:3796–3827. Reprinted with permission. John Wiley and sons

have excellent properties, and if you are delivering 20 drugs per antibody instead of three or four, you have much more efficient delivery.”

Mersana’s third-generation, fleximer-based ADCs could also allow targeting of tumours with lower antigen expression levels. The company has demonstrated this using HER2-expressing tumour models that express 50,000 antigens rather than the 500,000 commonly found in the patient population. According to Lowinger, “When we use the same antibody as Kadcyla, but attach with our technology 20 drugs, we can see that even low-expressing tumours are now highly susceptible, so that one can get completely tumour-free survivors in those same models that are completely non-responsive to Kadcyla.” This proof of principle clearly shows the potential for future ADC technologies.

Innovations are also underway in targeting. Moving away from large immunoglobins towards something smaller could provide better penetration into solid tumours, and a variety of approaches are being developed to achieve this. Improving the specificity of targeting tumour cells is another area of major interest. Engineered bispecific monoclonal antibodies (BsMAbs) – artificial antibodies composed of fragments from two different antibodies – make it possible to target two different antigens on the same tumour. Another strategy is to use BsMAbs that recognise antigens on a tumour cell and also activate the patient’s own T-lym-



phocytes, which can then destroy the tumour cell. This strategy is already being used with antibody therapies such as TRION Pharma’s Removab (catumaxomab), the first bispecific to receive European approval, for treating malignant ascites in patients with metastasising cancer and Amgen’s Blincyto (blinatumomab), which last December became the first bispecific antibody to be approved by the FDA, for use in patients with relapsed or refractory B-cell precursor acute

lymphoblastic leukaemia.

ADCs are sure to play a big part in the future of cancer therapeutics. As ADC development expands to target more tumours, Mersana CSO Lowinger suggests “there may be the ability to move away from conventional untargeted chemotherapy completely.”

At present, Adam Gibb thinks, with cancers such as Hodgkin lymphoma, the key will be learning how to identify the 10–30% of patients who will

**“We are looking at being able to have
a third bite at the potentially curative cherry”**

relapse following conventional therapy, and would benefit from a targeted approach early in their disease course. ADCs, he says, may be better able to destroy slower growing cancer cells that are more resistant to chemotherapy, and most likely to be responsible for relapse and refractoriness.

Costs and benefits

But the elephant in the room is the cost of these new drugs, which are expensive to develop. The number of ADCs gaining regulatory approval is likely to accelerate, with over 100 now in the pipeline. There have already been cost issues with Roche's Kadcyla. It has been approved for reimbursement in France and a number of other European countries, but the UK's NICE ruled that Kadcyla, with a full list price of £90,000 per patient, was too expensive for NHS use (in some cases it can be prescribed via the UK's Cancer Drug Fund). Amgen's Blincyto, meanwhile, represents a new record for cost of cancer treatment in the US, with a price tag of \$178,000 per patient.

Richard Sullivan, director of the Institute of Cancer Policy at Kings College London and former clinical director of Cancer Research UK, says: "The question you have to ask is: are antibody–drug conjugates going to be clinically meaningful? – I suspect a lot of them will not." He argues small incremental improvements from trial data may not translate into decent improvement in clinical outcomes, and these drugs are likely to fail or sit very near the bottom of economic benefit assessments. Adam Gibb suggests that more of a case can be made for an ADC such as Adcetris (which is also funded in the UK through the Cancer Drug Fund), which benefits a small group of mainly young

patients (around two hundred a year in the UK), who relapse after chemotherapy and stem cell transplants. It is still an expensive drug, says Gibb, but "we are looking at being able to have a third bite at the potentially curative cherry." He adds that the costs of the drug are still less than those associated with the donor stem-cell transplants given to this group of patients.

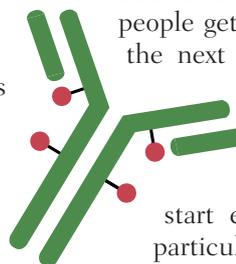
Problems with the high price of the branded drugs could also be compounded by potential problems surrounding development of ADC biosimilars – approved copies. Due to their molecular complexity and reliance on an originally cloned antibody, there are concerns that it may not be possible to produce copies without going through the entire development process again, "This could essentially kill any form of generic...so this is a double whammy," says Sullivan, as without competing generics, prices are likely to stay high.

The arriving wave of ADCs is illustrating a wider issue, says Sullivan: "They are just one technology amongst a massive tsunami that is hitting healthcare." He argues that there is a growing divergence and disconnection between the pharmaceutical industry's business model,

public expectations, and what in reality is affordable for Europe's healthcare systems, which is leading to massive inequalities and irrational prescribing. He expects other European countries will move in the UK direction: "It would not surprise me if people get much much tougher over the next two to three years about

what drugs are prescribed," he says, adding that pharmaceutical companies will need to start engaging in "fair pricing", particularly with medicines that provide relatively small incremental advances in health outcomes.

As Sullivan put it, ADCs give us "the beautiful science versus the messy dirty reality of socio-economics". On the scientific and clinical side, after a decade of development, antibody–drug conjugates now promise a new generation of targeted chemotherapies that may be able to tackle relapsed and refractory cancers, untreatable by conventional means. While not free of side effects, these new drugs do promise a milder, more tolerable form of therapy. But if ADCs are going to benefit the widest possible group of patients, a rational rethink of how we pay for them will need to take place. ■



CANCER WORLD JOURNALISTS' GRANT SCHEME

This article originated in a proposal submitted by the author for consideration for a *Cancer World* journalists' grant, a scheme set up to encourage journalists working in print, broadcast or online mass media to tackle more complex, multi-source, analytical articles that explore systemic issues that have an impact on patients. Further information about the grant can be found at cancerworld.org/Media/Journalist_Grants.html.



Side effects of targeted treatments: clinicians' perceptions, patients' realities

PETER MCINTYRE

The side effects of targeted drugs are poorly documented, and their impact on patients frequently seriously underestimated and undertreated. Efforts to address these issues could improve survival as well as quality of life.

The image of an exhausted patient with bald head and pale drawn face has almost come to 'represent' treatment with chemotherapy, the visible sign of interior pain and discomfort.

The language of targeted treatments has a different imagery. The rational approach, precision medicine and designer drugs constitute magic bullets attacking the cancer without harming 'innocent civilians'. Patients treated with these therapies will not just do better – they will look and feel better.

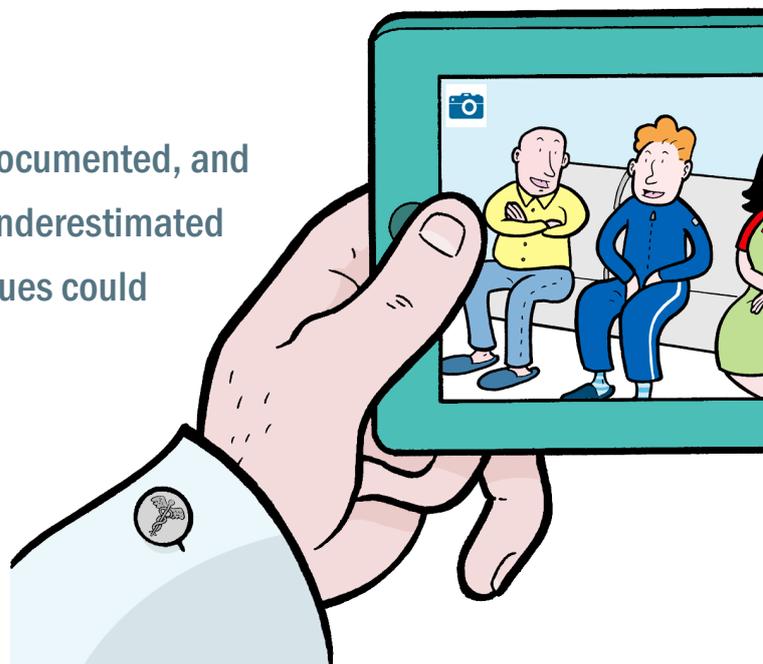
Therapies designed to block pathways that allow cancer to invade cells or that boost immune defences do indeed cause less harm than cytotoxic drugs, but that does not mean there is no collateral damage. A range of side effects are reported by patients – neuropa-

thy, tiredness, bone pain, nausea, persistent diarrhoea (or constipation), persistent headache, skin rashes, mouth ulcers and others. In

some cases a reaction may even indicate that the drug is having a positive impact.

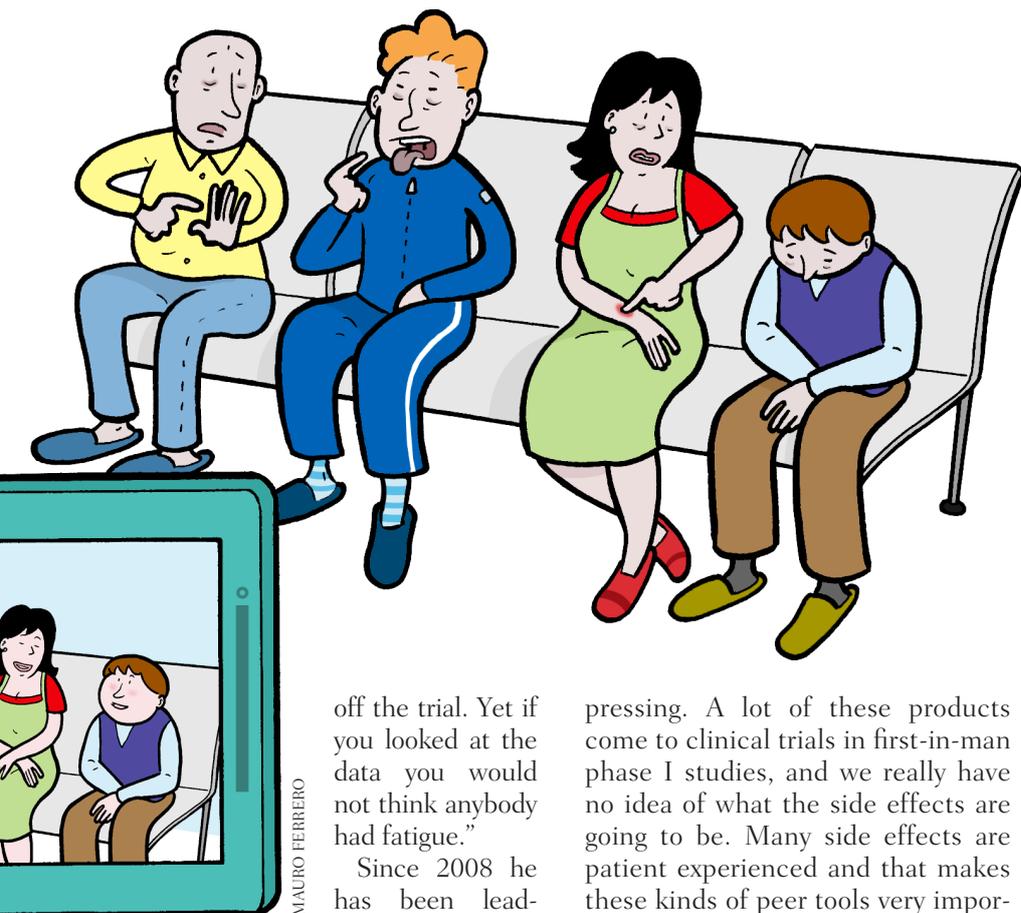
However, adverse effects do not always emerge during research trials where patient numbers are small, or in trials on patients with advanced disease, where the focus is on survival.

Most targeted therapies are self-administered, and in the case of successful treatments may require a patient's commitment for months or years. But if patients are given no information about what to expect, or support to alleviate symptoms, they may interrupt treatment without their doctor being aware of it.



The information gap

Ethan Basch, Director of the Cancer Outcomes Research Program at the University of North Carolina, has long campaigned for the patient perspective to be included in research. "Early in my career, it was very obvious that we were under-appreciating the impact drugs were having on people's day-to-day experiences," he says. "I recall an early phase II clinical trial where the physicians and nurses recognised that almost every patient had very severe fatigue and that was the reason why almost everybody went



MAURO FERRERO

off the trial. Yet if you looked at the data you would not think anybody had fatigue.”

Since 2008 he has been leading a US National Cancer Institute process to adapt a clinical tool to give patients an input, through a patient-reported outcomes version of the current Common Terminology Criteria for Adverse Events (PRO-CTCAE). This is a web-based platform to collect patient reports of treatment symptoms, asking about frequency, severity, and interference with daily activities. So far, 80 symptoms have been converted using patient-friendly terms such as “aching muscles”.

Basch hopes it will be widely used: “Targeted therapies make the need for this kind of tool much more

pressing. A lot of these products come to clinical trials in first-in-man phase I studies, and we really have no idea of what the side effects are going to be. Many side effects are patient experienced and that makes these kinds of peer tools very important for product development.

“Oral outpatient medications depend on people being compliant or adherent with taking the product, and we know from multiple studies that people who experience a lot of symptomatic side effects stop taking drugs.

“For me the advent of oral biologics as targeted therapy has strengthened the argument for patient-recorded tools to measure toxicity. There is an opportunity in the post-marketing stage to collect this information in the real world and use it to guide symptom management and clinical practice. We need to educate patients so they know what to expect.”

Dying from cancer or living with it?

A critical factor in willingness to tolerate side effects is the patient perception of what the drug offers in terms of survival and remission.

People with chronic myelogenous leukaemia (CML) today have such good survival prospects on imatinib and other TKIs that quality of life issues become very important.

The CML Advocates Network (cmladvocates.net) conducted a study of more than 2,500 CML patients in 79 countries, which highlighted how some patients have put the stability of their response at risk. Jan Geissler, co-founder of the patient network, says: “Many patients decide not to take their drugs as prescribed, to reduce fatigue, gastrointestinal issues and skin issues. The side effects don’t kill people, but over a long period can make them feel unhappy, especially since most CML patients do not experience symptoms before diagnosis.”

Geissler notes that the average age of CML patients on phase III trials was 47 while the average age of real world patients in Europe is nearer 65. “Phase II and III studies usually do not uncover low-grade side effects, because they may occur in an older population with comorbidities or are not recorded well. It is over the long period you see them.”

There can also be unexpected reactions. About 7% of patients on dasatinib need water to be drained from tissue around the lungs, while on another drug there is increased risk of heart damage to older patients who

“The advent of oral targeted therapies has strengthened arguments for patient-recorded tools to measure toxicity”

“Many patients don’t take their drugs as prescribed, to reduce fatigue, gastro-intestinal issues and skin issues”

have existing cardiac conditions.

At the other extreme, patients with advanced melanoma, which has a very poor prognosis, may see a dramatic improvement from BRAF and MEK inhibitors, although these drugs can also cause fatigue, thinning hair, skin rash or sunburn (one group of patients on vemurafenib refer to themselves as “vempires” because

they have to shun daylight!)

Molecular biologist Bettina Ryll lost her husband Peter to melanoma and now runs the Melanoma Patient Network Europe (melanomapatient-network.eu.org). “By the time my husband had his diagnosis in March 2011 the tumour was already very large. It grew at an amazing speed down his arm and basically encased his elbow joint – you would wake up in the morning and could see that the tumour had grown. He had a lot of pain.”

Peter Schoonjans joined a trial of the MEK inhibitor trametinib in London in 2011 and almost immediately the tumour started shrinking at the same speed as it had grown. Bettina Ryll said that side effects – rash, dry skin, joint pain and hair loss – seemed trivial compared to the miraculous benefits.

“He needed less pain killers; he could move his arm and his hand again. His quality of life was so much better. I thought people were exaggerating when they talked about side effects.”

Peter Schoonjans developed resistance to the drug and died less than a year after diagnosis. Nevertheless trametinib gave the family precious time and golden memories. “We were in a situation where it was very clear he would not live and you make allowances for that,” Bettina Ryll said. You are glad of every week you get out of it.”

She now understands better how patient experiences can differ. She recalls how the co-founder of the Melanoma Patient Network Europe (who has since died) suffered with the BRAF inhibitor vemurafenib. “I

remember thinking how different our perceptions were of the same class of drugs. Patients like my husband were above all grateful; seeing the tumours regressing was magical and we just treated the side effects. Patricia was on the drug for longer and had severe joint pains which seriously affected her life. She was much less enthusiastic. I see patients starting these drugs earlier and earlier, some before they have symptoms. They feel healthy and when they take the drug all of a sudden they have problems.

“My take home message is: don’t trust anyone but the patients. Everyone else is making assumptions. I even include myself in this.

“Fear of side effects or long-term side effects or lasting disability is a luxury for people who have many years left or who have not understood yet that they probably will not be fortunate enough to live to develop these.” Such patients often focus on immediate problems: pain, exhaustion, trouble with walking or with their hands.

The Melanoma Patient Network Europe conference in Brussels in April will focus on risk – including the risk of being over cautious and hindering the introduction of new treatments. “We need drugs for patients not drugs for healthy people,” says Ryll.

But she also sees the risks of adverse events, pointing out that drugs with fewer side effects are more cost-effective as they lead to less waste: “If the side effects become intolerable, people stop taking the drug to give

ADDRESSING LANGUAGE BARRIERS

The terminology drawn up by the US National Cancer Institute for the standardised classification of adverse effects of drugs used in cancer therapy has been ‘translated’ into everyday language to enable patients to use the system for reporting on their own side effects. Of 790 adverse events listed, 78 were deemed suitable for patient self-reporting, along with characterisations of the severity or frequency of symptoms or the extent to which they interfere with everyday activities.

Examples include:

Mucositis oral	Mouth or throat sores
Fatigue	Numbness or tingling in your hands or feet
Pruritus	Itchy skin
Rash acneiform	Acne or pimples on the face or chest
Arthralgia	Aching joints (such as elbows, knees, shoulders)
Myalgia	Aching muscles

The full list was published last year in the *Journal of the National Cancer Institute* JNCI 2014, 106 (9):dju244

them the space to function, and this becomes more important the longer the treatment. Who wants to be the one who always falls asleep during dinner with friends or at your kid's school performance?

“Initially, I naively thought all cancer patients took their drugs, but most of our patients have pills left over before they die and these must come from somewhere. Drugs don't work in patients who don't take them.”

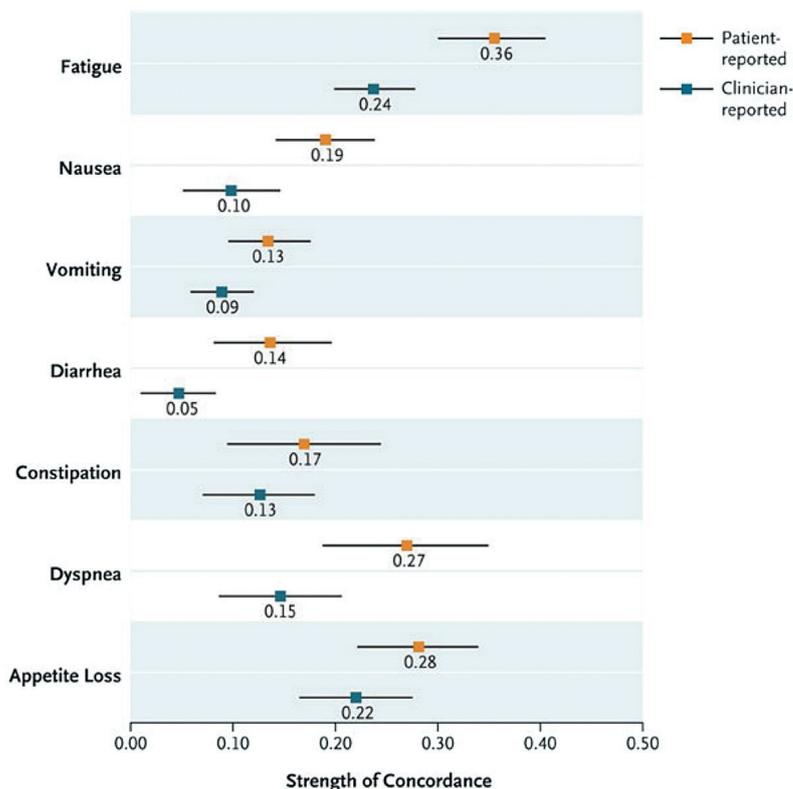
Patient-collected data

In 2009, a survey conducted by Myeloma Patients Europe (mpeurope.org, then Myeloma Euronet) showed fundamental differences in perception between myeloma patients, nurses and doctors in assessing the impact on quality of life of various side effects, including hair loss, fatigue, reduced body function, neuropathy and thrombotic events (<http://tinyurl.com/side-effects-perception-survey>). In 2014 an Italian study (*Haematologica* 2014, 99:788–793) showed that physicians tend to underestimate the impact of fatigue, muscle cramps and musculo-skeletal pain, compared to the perception of CML patients.

Ryll's advice, “don't trust anyone but the patient” is at the core of advocacy by Susan Love, a former breast cancer surgeon who heads her own research foundation based in Santa Monica. Partly informed by her own treatment for cancer, she is increasingly focused on quality of life issues and “the new normal” after treatment.

“As a physician you compare the patient who is alive to the people who

PATIENTS' vs CLINICIANS' ASSESSMENTS: CORRELATION WITH QoL



Patients' self-assessment of adverse events consistently correlate better with their overall health status than clinicians' assessments, according to the findings of a study done at New York's Memorial Sloan Kettering Cancer Center, involving 467 people with breast, lung, genitourinary, or gynaecologic cancers over a total of 4034 clinic visits. Adverse events were recorded using the NCI's Common Terminology Criteria for Adverse Events; overall health status was measured with the EuroQoL EQ-5D, adjusted for a US population.

Source: Ethan Basch (2010) *NEJM* 362:865–869 © 2010 Massachusetts Medical Society. Reprinted with permission

have died and you pat yourself on the back. But as a patient, although you are happy to be alive, you compare yourself to the person you were and are acutely

aware of the price you have paid. “I don't want to downplay the success of treatment. But we should not act like everything is back to normal

“My take home message is: don't trust anyone but the patients. Everyone else is making assumptions”

“The purpose is to learn a little bit more about who is getting what so maybe we can avoid it or anticipate it”

and great. We should recognise that in some ways it is like the military coming back from conflict with post-traumatic stress disorder.”

In October 2012 the Dr. Susan Love Research Foundation launched the Health of Women Study (healthofwomenstudy.org), as an online cohort study open to healthy women as well as women who have had cancer.

The study has been informed by a collateral damage project which attracted more than 9,000 responses from 3,200 women. By the end of 2014, almost 52,000 women had registered for HOW, of whom approximately 10,000 have had breast cancer.

The quality of life questionnaire (live on the website) asks about exercise, lifestyle, medical history, and environment. The results from women who have had breast cancer treatment and from women who have never had cancer may shed some light on symptoms driven by normal aging and symptoms connected with the cancer or the treatment.

Love says: “The medical profession say all the time that new drugs don’t have side effects like chemotherapy, and that is right – they have different side effects. Herceptin is the poster child of targeted therapies for breast cancer and that certainly has side effects.

“My goal is not to trash the treatments or the drug companies. The purpose is to learn a little bit more about who is getting what so maybe we can avoid it or anticipate it.”

This is a study of self-selected

women, but Susan Love says that its size irons out any biases. “Most patient-reported outcomes include 100 or 200 people – we have got 10,000. I think we are more representative than the usual patient-reported outcome study in one hospital or medical centre.”

Jan Geissler makes a similar point for the CML Advocates Network. “We recruited 2,500 patients into our adherence study within three months, which is tenfold the number in any adherence study that professionals have done.”

The nurse role in supporting patients

Nurses play a critical role in identifying and treating side effects. Christine Boers-Doets is completing a PhD at Leiden University Medical Centre in the Netherlands, looking especially at skin and oral cavity problems associated with targeted therapies.

“A huge number of cancers are treated with targeted agents, and therapy is discontinued or doses adjusted on a regular basis, even with non-life-threatening side effects. I don’t understand why, as the side effects disappear even if you continue with the therapy. I have learned that it is possible to get rid of them and avoid a grade 3 reaction when patients know how to take care of their skin and mucosa. With appropriate management most adverse events can be managed without dose modification or discontinuation.

“For example, patients need to use an unscented cream from the start of

treatment at least twice a day to prevent skin reactions. But they often start treatment too late and are given ointments which do not hydrate sufficiently or lotions which dry out.”

Boers-Doets developed the TARGET system (Terminology, Assessment, Reporting, Grading, Education, Treatment), to delineate the assessment, grading, and management of dermatologic and mucosal adverse events in a busy clinical setting or research protocols.

“Skin and oral effects can be severe if not treated at an early stage. Chemotherapy can cause a hand-foot syndrome (palmar-plantar erythro-dysaesthesia) while targeted therapy can cause a hand-foot skin reaction. They look the same but require different treatment approaches.

Boers-Doets regrets the lack of clinical trials focused on side effects of targeted cancer treatments, and she has established the IMPAQTT Academy for healthcare professionals and the IMPAQTT Foundation (<http://impaqtffoundation.com>), directly focused on patients and their social support system.

She is developing case studies from her research and by sharing experiences with other specialist nurses. She gives the example of a patient taking Tarceva (erlotinib) for lung cancer, who developed severe and distressing crusts on her scalp, a condition not mentioned in the literature. She discussed treatment with a specialist and the patient’s doctors, and when some nurses attending her lectures said they had also seen

scalp crusts, she began developing a case report on the condition and how to treat it.

Boers-Doets says that patients on new therapies need to be seen very regularly at first – perhaps twice a week – until they can manage their own conditions. “Patients go to the pharmacy to pick up their targeted therapies and often stop after a couple of days because of side effects they did not expect. The remaining drugs are discarded. We throw millions of euros away because there is not enough counselling during the first two cycles of therapy.”

The nurse role is valued at the UNC Lineberger Comprehensive Cancer Center in North Carolina, where Ethan Basch and colleagues work with nurse navigators who advise patients in the clinic and call them at home.

Geissler finds nurses to be a great source of information for CML patients too. “They understand skin rash and gastro-intestinal issues and that has been extremely helpful in how we provide information, so patients and carers can manage it themselves.”

The patient voice is also becoming better heard in clinical research across Europe. The European Medicines Agency finished consulting in November 2014 on a paper calling for quality of life data as perceived by the patient to be included in research protocols, agreeing that “objective clinical measures may not necessarily correlate to a patient’s own feeling of wellbeing.” ■

UNDER-ASSESSED AND UNDER-TREATED



These images show how many different ways targeted drugs can affect the skin, yet medical teams often lack training in awareness and assessment of these toxicities, and the evidence on the specific ways each needs to be treated. More detail about how to assess and manage these sorts of skin toxicities is available in the e-grandround published in *Cancer World* (March–April 2013) and as a recorded webcast on e-eso.net (Past Programme). Skin toxicities are only one of many troublesome side effects associated with different targeted medicines, which include tiredness, aching bones and muscles, diarrhoea, constipation and other gastrointestinal symptoms, persistent headache, mouth ulcers and more.

“We throw millions of euros away because there is not enough counselling during the first two cycles of therapy”

Generic cancer drugs that we can trust

MARC BEISHON

Generics markets are gearing up for the expiry of patents on some of the first targeted cancer drugs. It's good news for greater access, but patients want reassurance that switching to generics won't put them at risk.

Generic drugs are a huge and complex part of the health-care market. Each year, dozens more become available as the patents that protect exclusive marketing rights for the originator drugs expire or are circumvented, and as developing countries gear up their pharmaceutical sectors.

Cancer drugs are no exception. According to recent figures, in a total global oncology drugs market approaching \$100 billion, revenues from generics are growing at twice the rate of the market as a whole, and will

reach more than \$20 billion by 2018. The vast majority of all drug prescriptions are already for generics – more than 80% in the US, for example.

The market is complex for several reasons. One is that rules for marketing exclusivity for medicines, e.g. for orphan drugs (for rare diseases), vary across countries, giving rise to a patchwork of opportunities for generics. Indeed in India there has been a direct challenge to drug patents, the notable case being for imatinib (Gleevec). Then there is the economics of producing generics. With prices for some

reduced to just a few cents a dose, incentives to remain in production can disappear, which is one of the contributors to well-publicised shortages of cancer drugs in recent years.

And there are concerns about the quality of generic drugs. While most of the small-molecule cancer agents are straightforward to produce, they may be produced in facilities that differ from those of the originator company in levels of quality control and





like imatinib and chemotherapies like cisplatin on the one hand, and large-molecule ‘biologics’, such as monoclonal antibodies, on the other. The latter cannot be copied in the same way as small-molecule agents, and are part of a growing interest and market in ‘biosimilars’, which have more demanding regulatory requirements.

However, there is also a growing category in-between, so-called complex non-biological drugs, which also cannot be subject to conventional generic regulation. A good example in cancer is Doxil, which is a nanotechnology formulation of the chemotherapy drug doxorubicin, and was introduced in 1995. Here the drug is encapsulated in nano-sized liposomes, so assessing the equivalence of a generic version poses challenges concerning the size and behaviour of particles. In 2012, the US regulatory body, the FDA, rapidly approved a generic version of Doxil to ease a shortage of the drug. However, questions about how regulators approve follow-on versions of drugs with novel delivery mechanisms and multiple agents are still the subject of discussion.

Quality control

The vast majority of generic cancer drugs today are small molecules that have been subject to relatively simple regulation for a single active ingredient. For oral drugs, regula-

tors look for evidence that the drug is ‘bioequivalent’ to the original through tests on bioavailability, which is the amount of the drug that reaches the bloodstream – the tests measure the rate and extent of absorption, and bioequivalence is shown by testing both the generic and the original in small groups of people, usually healthy male volunteers. Drugs delivered intravenously are usually exempt from bioequivalence tests, as it is assumed that all the drug is reaching the bloodstream.

Regulators also look for data on the manufacturing process and stability of the drug, to ensure compliance with the general regulations concerning good manufacturing practice (GMP) that apply to any drug. Other than that, a generic small molecule faces far less stringent regulation to reach the market than does the original agent, which will have been required to go through clinical trials to demonstrate good evidence of efficacy and safety in patients with the target disease.

Atholl Johnston, professor of clinical pharmacology at Queen Mary, University of London, says that doctors and patients can be confident that most of the generic drugs that are dispensed in Western nations are of high quality. The manufacturing plants are inspected frequently, he says, and the dossiers submitted to the European Medicines Agency (EMA) and other regulators for approval will tick all the right boxes for bioequivalence and safety factors. This is borne out by a 2009 review

also in the amount of active and other substances used to make up a pill or an injectable dose.

A clear distinction can be made between small-molecule drugs, such as tyrosine kinase inhibitors (TKIs)

“Doctors and patients can be confident that most generic drugs dispensed in Western nations are of high quality”

“Globally there are many generic drugs for which companies offer little or no support and monitoring”

of 12 years of bioequivalence data from the FDA of more than 2,000 studies of approved oral drugs, which showed the criteria used have been working well (*Ann Pharmacother* 2009, 43:1583–97).

“But there have been problems with both branded and generic drugs,” Johnston notes. “Recently there have been several recalls for Tylenol [paracetamol] products in the US, and the FDA has also uncovered many shortcomings in the major Indian generics maker, Ranbaxy, such as signatures on quality documents of people who are on holiday and falsification of drug stability data.” In 2013, Ranbaxy’s US arm had to pay fines and claims totalling \$500 million relating to the manufacture and distribution of certain adulterated drugs made at two of Ranbaxy’s manufacturing facilities in India, the US Department of Justice reported.

Johnston adds: “All drug regulation is based on trust and what companies tell you – and if we go looking for problems we will find them.” Harmful contamination may be unusual in products made in or supplied to Western nations, but they can reach patients, such as in the UK where an intravenous feed caused a bacterial infection that killed three premature babies in 2014. In India last year a number of women undergoing sterilisation died after receiving antibiotics contaminated with rat poison – developing countries face greater risks from lower standards, but many generics that are used in the West are made in

plants in countries such as India.

Impurities, excipients (the many different substances such as preservatives and coatings that the active ingredient is packaged with in a pill or vial), and the amount of active agent itself can all have an impact on the efficacy and side-effects of drugs, adds Johnston, and the approval of oral generics mainly depends on meeting an acceptable range of activity compared with the original drug, not an exact match. Dossiers submitted to the EMA do have to disclose impurities, and the EMA also asks for ‘pharmacovigilance’ follow-up of generics, but globally there are many generic drugs for which companies offer little or no support and monitoring, and regulators don’t require generics to undergo phase IV post-marketing studies.

A number of classes of drugs, including those used in oncology, have a narrow therapeutic window (a narrow dose range where the drug is effective but not too toxic). The potential variation in a generic could therefore result in a patient receiving a less than optimum dose – or too much. There are few studies on variation in more than a few generic cancer drugs, but Johnston points to one carried out by a French team that compared the quality of generic formulations of docetaxel available in emerging countries – docetaxel is a chemotherapy drug widely used in a number of tumours including metastatic breast cancer (proprietary name Taxotere, from Sanofi).

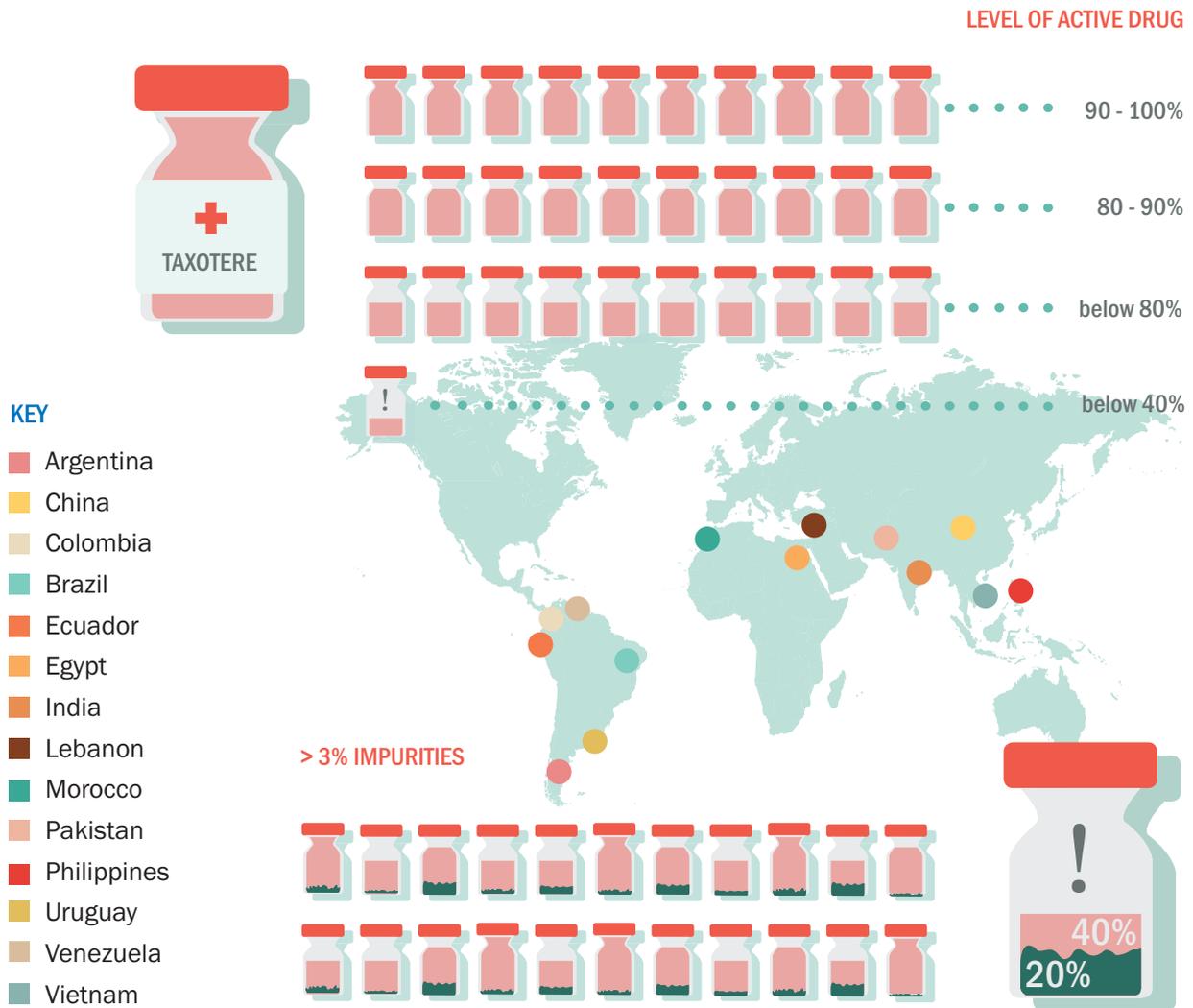
Wide variations

The researchers acquired 31 versions of docetaxel in 14 countries including Brazil, China, Egypt, India and Vietnam, demonstrating the large number of generics that can be available for one agent (at the time of the study generic docetaxel was not yet available in the US, Japan or Europe as it was still on-patent). Using Taxotere as the reference, they found that 21 generics contained less than 90% docetaxel, 11 of which had less than 80% of what would be expected. Only 10 were in the acceptable range of 90–110%. They also measured impurities, setting a conservative limit of 3% (the reference was 1.6%). They found that 23 of the generics had impurities levels of more than 3%, and many of the impurities were not detected at all in the reference drug, although this study could not identify what these substances were (see *Curr Med Res Opin* 2008, 24:2019–33).

One of the generics, from India, had a docetaxel content of less than 40% of the reference drug and a 20% level of impurities, showing just how poor they can be. The authors conclude: “The number of generic docetaxel formulations failing to meet internationally recognised quality criteria is a concern, in particular given the potential clinical consequences of patients receiving a lower dose of docetaxel than expected.” They also note that the findings were in line with studies of other types of generic drugs, such as for ciprofloxacin and clarithromycin (both antibiotics) and clopidogrel (which prevents blood clotting).



ACTIVE DRUG LEVELS AND IMPURITIES IN 31 GENERIC VERSIONS OF DOCETAXEL IN 14 COUNTRIES



A 2008 study of the chemotherapy docetaxel (original drug, Taxotere), produced in a variety of developing countries when the drug was still in-patent, showed why governments need to protect patients from sub-standard generics by effective regulation. The study, which found unacceptably low levels of active drug in 21 of the 31 generic versions and >3% impurities in 23 of the 31 was funded by Sanofi, which manufactures Taxotere.

Source: J Vial, M Cohen M, P Sassi et al (2008) *Curr Med Res Opin* 24:2019-33

One generic had a docetaxel content of less than 40% of the reference drug and a 20% level of impurities

“You can’t do effective pharmacovigilance if you keep switching among a number of generics”

Since the study was published, docetaxel has come off patent, and the quality in emerging markets may have improved, and different products will be available, but it shows what can happen in countries with poor regulation, where a generic drug may border on being counterfeit. It’s hard to get a picture of the market because, although countries should have their own database of authorised agents, there is no public global database of generic drugs that could make their way into various supply chains, often rebranded by other suppliers.

A recent clinical study on docetaxel, carried out in Canada on a population of breast cancer patients, compared just one generic with the original. It found little difference in adverse events, bar quite a large increase in

grade IV febrile neutropenia in the generic group (see *Ann Pharmacother* 2014, 48:447–455). But this drug is likely to be of high quality, given it is on the Canadian market, which is said to have one of the world’s best bioequivalence inspection regimes.

Also last year, the FDA issued a warning about an adverse effect from docetaxel. The drug is administered in a solvent containing ethanol (alcohol) and has been issued in two vials, one containing the solvent, that are mixed before administration. In 2009, Sanofi introduced a single-formulation already prepared with alcohol, which had the effect of doubling the alcohol content over the two-vial preparation; other generic suppliers of a single-vial docetaxel can have even more – Pfizer’s preparation has

over three times more.

This might seem relatively trivial, but the FDA references a letter by two oncologists in the UK who found a male patient receiving palliative care showed symptoms of alcohol intoxication with the new formulation. They point out that alcohol behaves differently when injected rather than drunk, and in cases such as their patient it could render him unfit to drive, which may have led to him rejecting further chemotherapy, and for this patient there was also “a real risk of a relapse in alcoholism”. People may also have religious objections.

In Australia, Pfizer’s docetaxel application was withdrawn before a final decision by the country’s regulator, but it was about to be refused owing to both alcohol and propylene glycol content, and concerns about bioequivalence – in this case the regulator seemed to want a human study despite it being an intravenous drug (Pfizer did submit a study carried out on dogs). In contrast, the UK, which acted as a reference member for most EU countries, and the US have both authorised this generic.

For Johnston, this is just one of many examples of the difficulties that patients can face when they are switched to a new formulation or generic, often without warning or appreciation of differences that, while not necessarily intrinsically harmful, could have

CML PATIENTS ARE DEMANDING CONSISTENCY AND QUALITY

Following in-depth discussions involving groups from many countries, the CML Advocates Network set out its approach to the use of generic forms of imatinib and other drugs used by their members.

The statement, issued in August 2014, welcomed the greater patient access that generics can bring, but raised concerns “about the impact on their cancer when switched between different products for non-medical reasons, if these products’ equivalence in terms of quality and efficacy is uncertain”.

The statement called on governments, health authorities and healthcare professionals to minimise potential uncertainties and risks for patients with the following five measures:

- Provision of reliable proof of quality and equivalence of pharmacokinetics and bioavailability
- Collection of comparative clinical data to ensure comparable efficacy
- No switching for non-medical reasons if a patient is responding optimally and tolerating well
- No switching between products of the same compound more frequently than once a year to allow consistent follow-up, and in case of loss of response or increased toxicity, switch back or switch treatment
- More frequent monitoring (obligatory: PCR tests; optional: plasma level testing).

Source: www.cmladvocates.net/133-generics/354

a significant impact, for instance on adherence. Healthcare providers and pharmacists are often able to switch prescriptions between a number of generics, and patients only find out if they look closely at the packaging.

A primary motivation to dispense generics is of course cost, but Johnston says that if there are problems with drugs the savings could be wiped out. He has a particular interest in transplant drugs where, as he points out, the cost of rejection episodes and of losing a transplanted kidney owing to a poor drug could be great. “You have to ask whether a drug is mission critical – if so it’s a nonsense to keep switching among a number of generics as you just can’t do effective pharmacovigilance then.”

Patients want harmonisation and transparency

A group that is keeping a close watch on ‘mission critical’ cancer generics is the CML Advocates Network, which unites chronic myeloid leukaemia patient groups across the world. It has a dedicated section for generics on its website and has organised several sessions at conferences. As with so many other issues in oncology, it is the drug imatinib – the first TKI – that is the main focus. Imatinib has been copied extensively, and the network is surveying these generics, presenting the results in an ‘unofficial’ CML TKI register. Currently there are more than 60 imatinib and dasatinib generics – dasatinib (Sprycel) is another TKI used in first-line CML treatment – and there will more to come for var-

ious cancers, as other drugs come off patent or are even compulsorily licensed for generics.

In 2012, India compulsorily licensed one drug – Nexavar (sorafenib), a cancer drug – giving a generic maker (Natco Pharma) a licence to make it, as Natco argued that the patent holder, Bayer, had not adequately introduced the drug in India. In another high-profile case, India rejected a claim by Novartis for exclusive marketing of its formulation of imatinib, as generic versions were already on the market because the country did not recognise the patent system until 2005, and Novartis’ imatinib also did not meet the requirement of ‘enhanced therapeutic efficacy’. Currently, imatinib is made by ten generics companies in India.

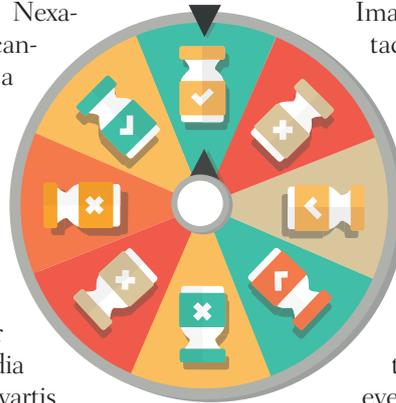
Šarūnas Narbutas, who is a CML patient active in the advocates network and in cancer advocacy in his home country, Lithuania, says there is concern that the molecular targeting of drugs such as imatinib poses particular challenges for assessing their efficacy and safety. “We just don’t have the long-term data about possible effects of different excipients and stability of these drugs, and in any case generic companies must use an alpha form of the imatinib crystal, at least until the patent expiration in 2019, whereas Novartis, the marketing authorisation holder for

Glivec, uses the beta form. Legally, they are ‘bioequivalent’ but they can produce different side-effects and clinical outcomes.”

Imatinib has been a spectacular success with CML, but it is a strong candidate for therapeutic drug monitoring to ensure that patients attain and maintain response, and Narbutas says people are rightly worried about putting their response at even the slightest risk if they are switched to a generic.

“Before imatinib generics came to Europe we had case reports from India that some patients who were switched to substandard versions had severe side-effects or lost response, and there have been conflicting studies since from Colombia, Egypt, Iran and Turkey.”

He notes that one of the largest ongoing studies so far is in Serbia, where all existing and new patients, about 220 people, were put on a generic imatinib called Anzovip without warning in 2012, much to the alarm of advocates in the country. Although supplied by a local company, the suspicion was that it is repackaged from an Indian provider, and it is much cheaper. But so far, concerns about its efficacy and safety have been unfounded, report Serbian haematologists, who are monitoring their patients closely. A few long-term patients did lose



The molecular targeting of drugs such as imatinib poses particular challenges for assessing their efficacy and safety

Advocates are not against generics, but there must be much more transparency and information about their use

cytogenetic response and were switched to nilotinib (Tasigna), but most patients followed up so far have seen equivalent responses to Glivec and no different toxicity after 18 months. Another year's data is needed, Narbutas adds, but ideally Serbia's CML patients would have liked to have had the drug independently tested by the government at a European laboratory.

"There are similar issues with TKIs for other cancers, and also for biosimilars," says Narbutas. "You need to be closely followed up to see whether you are responding in the same way as if you were taking the originator drug, and we strongly advocate not to keep jumping between generics; you should stick to one generic for at least a year to allow for comparable medical history in each patient." The key point is that advocates are not against generics given that they open up access to key drugs, but there needs to be much more transparency and information about their use, and effective regulation on efficacy and safety. CML advocates in Canada note that patients can be switched to a generic by pharmacists and their oncologists may not know unless the patient tells them. A recent review of generic imatinib in Canada and the EU does provide reassurance, finding there is no evidence of less effectiveness (*J Oncol Pharm Pract* 2015, 21:76–79).

And it is not just poorer nations that can benefit from generic cancer drugs. A recent study in the US

found that women taking hormone therapy for receptor-positive breast cancer are more likely to continue treatment on generics owing to lower out-of-pocket costs.

There is research at stake too, as cancer generics are increasingly in demand not only for standard treatments but also for clinical trials. In a number of cases the original marketing authorisation holder may not even be in the market anyway. This places more responsibility on the major generics firms to provide education and support for their products, and transparency about quality processes. Johnston mentions a South African generics firm that rejected an approach to produce a drug under contract, when it was asked to cut the number of quality control steps it takes – there can be 40 or more such steps. Narbutas adds that advocates who have been invited to see how Glivec is made by Novartis were impressed by the extent of the quality control, and inevitably this raises questions about smaller companies with fewer resources.

But the market remains confusing, and there are no guidelines for patients about the issues arising from switching to and among generics. While the world's drug regulators are mostly in agreement about the bioequivalence approaches used to assess generic drugs – there are more similarities than differences, as a review found (*AAPS Journal* 2013, 15: 974–990) – patient groups want more regulatory harmonisation.

Signs of progress

Two recent initiatives may help. In 2012, the International Generic Drug Regulators Pilot (IGDRP) was launched to develop a more global picture, and recently the European Union has announced it will lead a project within this using the EU's decentralised procedure "as a model to accelerate the assessment of applications for generic medicines", one of the pilot's work packages.

Then in 2013, the EMA, FDA and some EU member states said they would start sharing information on inspections of bioequivalence studies submitted to them – a move that advocates had pushed for at a meeting at an ASCO conference, according to Narbutas. The collaboration also includes inspections of facilities where the studies are carried out.

It is early days for these projects and India is notable for its absence so far from the international pilot, and is not yet an observer at the longer standing ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use), which is led by Europe, the US and Japan.

However, the recent focus on generics at international level is encouraging, though an overriding issue is that countries may have to pay more for high-quality generics rather than driving the prices down to levels where some companies will cut corners. ■

Knocking at the door of the global agenda setters

ANNA WAGSTAFF

The World Oncology Forum is challenging global policy makers to face the reality that current approaches to controlling cancer are not fit for purpose.

An invitation to Davos shows they may be listening, but do they yet understand the need for change?

When the World Oncology Forum first convened in Lugano three years ago to debate the question “Are we winning the war against cancer?”, it was intended to be more than an academic exercise.

The date was October 2012. New statistics from the Global Burden of Disease, set to appear in *The Lancet*, would shortly confirm that cancer and cardiovascular disease had become the top two global causes

of death. Researchers at the WHO’s International Agency for Cancer Research had recently published a study showing that, by 2030, annual death rates from cancer would rise by almost 60%, to 13.2 million people, with the lion’s share of the burden falling on the developing world. Optimism about the new targeted therapies was giving way to a more sober assessment about the size of the challenge of overcoming resistance. It all pointed to the need to evalu-



LUCA SANGIORGI



Debating strategies to defeat cancer at the World Oncology Forum. The text of the Stop Cancer Now! and other appeals issued by the Forum, and details of participants, can be found at www.worldoncologyforum.org



ate whether current efforts to control cancer were on track and, if not, to formulate new strategies.

The clue was in the name: the World Oncology Forum (WOF). Convened by the European School of Oncology in conjunction with *The Lancet*, this was envisaged as a disease-specific version of that other



Forum which gathers each January 160 km down the road from Lugano, at Davos. Like the World Economic Forum, WOF brought specialists (clinicians, researchers, epidemiologists) together with policy makers, advocates and industry for informed but informal discussions about how to respond to a serious global problem.

The exercise was also carried out with one eye on Davos, because developing a consensus within the cancer community would be a first step towards the bigger challenge of convincing the people with the power to deliver the changes that are needed. The World Economic Forum, with its mission of “improving the state of the world

through public–private cooperation”, was after all the setting where Peter Piot had convinced a group of pharmaceutical company CEOs to sign up to the principle of giving poor countries access to anti-retrovirals at an affordable price. The Global Fund to fight AIDS malaria and tuberculosis, and the GAVI alliance are also closely connected with Davos.

The Stop Cancer Now! appeal, launched from the first World Oncology Forum, echoed many of the points raised by earlier international initiatives – the Paris Charter Against Cancer in 2000 and the UICC World Cancer Declaration of 2008 – about national and international priorities, and about the importance of an integrated and planned approach, of data

Research required to develop innovative treatments that can tackle the problem of resistance is expensive and risky

and monitoring, and of evidence-based and locally appropriate solutions.

But it went further, in challenging prevailing assumptions and vested interests that continue to undermine efforts to mobilise a global response to cancer.

Stop Cancer Now! rejected the notion that unravelling the human genome and developing new knowledge about the molecular biology of cancer means that breakthrough treatments are only a matter of time. It characterised the business model for developing new therapies as “broken”, and called for “more efficient forms of public–private collaboration, geared to accelerating delivery of affordable therapies that are of real benefit to patients across the world.”

The appeal also rejected the notion that international efforts to address cancer in developing countries should be limited to promoting pre-

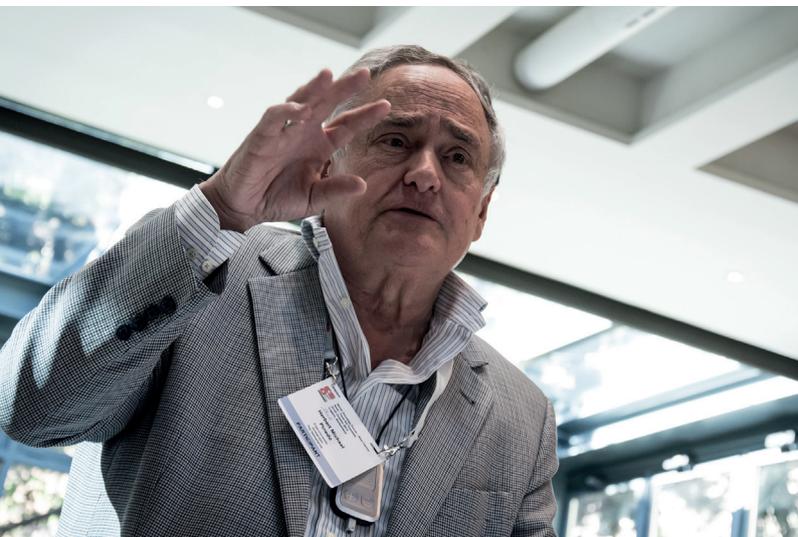
vention measures as part of a wider strategy to control ‘non-communicable diseases’. It called for all cancer patients to have access to “a package of indispensable diagnostics and curative and palliative care shown to get the best possible results within the local setting,” and linked this to “the promotion and strengthening of universally accessible health systems... driven by cost-effective ways to deliver the best results and not by vested economic interests.”

Last October, a second World Oncology Forum developed these themes.

Fixing the broken model

In an appeal to Speed up Progress Towards a Cure, participants at this second Forum united behind a call for academic, not-for-profit bodies to be funded to take on much more of the work of drug discovery and early development, on the grounds

SWISS-IMAGE.CH/BENEDIKT VON LOEBELL



LUCA SANGIORGI

Unique insights. Around 100 leading figures in cancer have participated in the World Oncology Forum. Pictured here is Bob (Herbert) Pinedo, a pioneer in medical and translational oncology, who now spends a lot of time helping develop screening programmes in his native Curaçao

that the research required to develop innovative treatments that can tackle the problem of resistance is expensive and risky. Continuing to rely so heavily on the commercial sector, which is inherently risk averse, would only prolong the succession of new drugs that only marginally delay the onset of resistance at increasingly unsustainable prices.

This appeal also called for a package of negotiated changes to the evaluation/approvals process, pricing mechanisms, and academic

Davos, January 2015. South African health minister Aaron Motsoaledi makes a point at the Crisis of Chronic Diseases session. Franco Cavalli, chair of the World Oncology Forum, sits to his right



incentives and rewards structures, to develop an ecosystem that encourages innovative and collaborative research, and aims high.

In a globalised world, all of these changes – pricing in particular – need to be discussed and agreed at an international level.

WOF also heard from Rengaswamy Sankaranarayanan, Special Advisor on Cancer Control at the International Agency for Cancer Research (IARC), about the impressive progress that has been made in a number of low- to middle-income countries. Participants concluded that meeting the needs of the 90% of the world's population who lack access to even the basics of early detection, treatment and care is above all a national responsibility.

It's up to governments to prioritise investment in cancer control, and to develop sustainable cancer services as an integral part of universally accessible health services. It is possible to protect quality and sustainability by ensuring that investment decisions are based on what can achieve the greatest benefit for the most people, services are delivered according to locally adapted evidence-based guidelines, and the whole system is effectively monitored.

A great deal can be achieved, even in the most resource-constrained countries, by prioritising early detection, basic diagnostics (X-ray imaging and ultrasound), high-quality cancer surgery, basic radiotherapy, generic drugs

from the WHO Essential Medicines list, basic supportive and palliative care, and data collection.

Well-trained primary care/community health professionals have a key role in prevention, early detection and delivering many types of supportive and palliative care. This is where combining cancer strategies with wider efforts to combat non-communicable diseases can pay off.

However, participants recognised that even with the best political will in the world, lower-income countries and those at an early stage of building a basic health service need help. So in addition to calling for action from national governments, a third appeal, Treat the Treatable, also called for some form of 'global cancer fund' or 'global cancer initiative' to provide advice and implementation support, including soft loans, and function as a platform for negotiating affordable access to expensive equipment and therapies.

Like the changes to research, evaluation and pricing systems, this initiative would also need to be discussed and agreed at an international level.

The content of these fairly detailed appeals was not simply nodded through by the Forum; it emerged from lively and inclusive discussions, and represented a strong consensus among the participants, who are leading cancer efforts in a variety of fields, countries and settings. The question was, would it find a ready audience beyond their ranks, among those who need to be convinced?

There was only one way to find out.

WOF called for some form of global cancer fund or initiative to provide advice and implementation support

The contrast between the approach taken to cancer and that taken to infectious diseases was quite stark

Beyond the world of cancer

By the time of that second meeting in October 2014, the chair of the World Oncology Forum, Franco Cavalli, had already put steps in motion to get cancer onto the agenda of Davos the following January.

The organisers had agreed to “try out” this new topic as a candidate for inclusion on the Davos 2015 agenda, and had duly tabled “Cancer: the next global epidemic” as a panel session at a pre-Davos meeting held in September in Tianjin, China. Cavalli was invited to participate.

Back in Switzerland, the feedback from the Davos secretariat initially sounded very optimistic. But what finally emerged following consultation with the major partners was essentially two sessions, both of them focused on “breakthroughs” in therapy: A New Era in the Fight Against Cancer, and Pathways to a Cure. Cavalli was also invited to attend a third session, on the Crisis of Chronic Diseases.

The agenda was, in effect, predicated on exactly the assumptions WOF participants were seeking to challenge – that we are on track for finding a cure, and that the global epidemic of cancer can be adequately dealt with through addressing prevention and lifestyle issues common to all non-communicable diseases.

So while Cavalli welcomed the invitation to participate, the discussions were framed in a way that made it hard to speak to the WOF agenda. “I did what was possible promoting the ideas when I was able to,”

said Cavalli, “but it was a very difficult environment to present what we want to achieve.”

The contrast between the approach taken to cancer and that taken to infectious diseases was quite stark. The titles of the latter sessions used words like “catastrophic”, and they focused on questions such as how to improve on the world’s “abysmal” initial response to the Ebola outbreak. A high-profile forum session was addressed by former UN General Secretary, Kofi Annan, as well as Margaret Chan, Director General of the World Health Organization, and the presidents of Guinea and Mali. A UN appeal for a \$1 billion fund was launched to support the efforts of the national governments of Guinea, Liberia and Sierra Leone.

Yet for all the pain, trauma and economic disruption caused by the Ebola outbreak, from the time it started in March 2014 to the week of the Davos meeting in January 2015, the death toll was around 8,800, the epidemic had plateaued, and numbers were falling in every affected country.

During the same period more than 6 million people lost their lives to cancer, and the numbers will keep rising in the absence of a serious global response.

So what next? “We need to go back and gather more political support,” says Cavalli, pointing out that many leading figures have already attended UICC World Cancer Leaders Summits, including the Chinese health minister Chen Zu, who has a background in cancer research.

The current President of Uruguay, Tabaré Vázquez, who has a background in radiotherapy, may be particularly well placed to build momentum behind calls for international action on cancer, says Cavalli, as Uruguay will chair the Community of Latin American and Caribbean States for the next two years. Vázquez spoke at a World Cancer Leaders Summit in 2008, and Cavalli hopes he will agree to proposals to give a high profile to the need for action on cancer in the developing world.

Building political support for efforts to change the ecosystem for researching and developing new cancer therapies, Cavalli believes, will be less of a challenge. “The high cost of cancer drugs is already such a problem that it will inevitably be discussed at a political level,” he says. However, he believes that it will be important to promote discussion in both the scientific and the lay media.

The UK *Financial Times* has already run a piece on this issue, to coincide with the Davos meeting. It included a lengthy quote from Paul Workman, head of the UK Institute of Cancer Research, which drew on ideas discussed at last October’s World Oncology Forum, where Workman presented a keynote speech. Given the importance of the pharmaceutical industry and the strength of the not-for-profit cancer research sector, the UK is one of the countries where this debate will be crucial in the coming years.

And as for Davos? We’ll be back says Cavalli. ■

Intratumoural drug metabolism and the disposition of anticancer agents: implications for clinical treatment

Pharmacokinetics within tumour cells play an important role in the development of resistance. A better understanding of the mechanisms involved is important for devising treatment strategies to extend tumour response.

We know that cancer cells develop acquired capabilities, including an ability to evade apoptosis, and develop insensitivity to anti-growth signals (*Cell* 2000, 100:57–70). We have less information, however, on how cancer cells are able to develop resistance to drug action by bypassing drug signalling and also decreasing drug levels at the target site.

Adsorption, distribution, metabolism and elimination (ADME) are the key processes underlying the pharmacokinetics (PK) of any drug, each of which may be changed during the development of resistance. The figure overleaf illustrates intratumoural ADME in the development of drug resistance, summarising how drugs can react in cells during cancer treatment. The starting point is a tumour, comprising a population of different clones, which is treated with a drug. Hopefully, a lot of the cancer cells go into apoptosis and die. However, there are often resistant clones that



European School of Oncology e-grandround

The European School of Oncology webcasts fortnightly 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, Bertrand Rochat, from the Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland, reviews the latest evidence on intratumoural drug metabolism as a mechanism of drug resistance, and he looks at the implications for clinical treatment with TKIs.

Daniel Helbling, of the Gastrointestinal Tumour Centre, Zurich, Switzerland, posed questions asked by the audience during the live webcast. Edited by Susan Mayor.



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

rapidly lead to primary resistance. In a second scenario there is selection of tolerant clones that will show growth stabilisation. These cells are apparently dormant, but in reality they are activating resistance mechanisms designed to help the cells overcome the action of the drug. After a few months or years, these dormant cells develop secondary resistance to the drug, so it is no longer effective.

The figure below shows two cell lines that illustrate different mechanisms of development of resistance to imatinib over one year. Resistance develops over different time periods in the two lines. The first cell line (KBM5) shows rapid development of resistance by selection of pre-existing resistant clones. After about 120 days, new clones appear with a mutation in the target protein for imatinib (Bcr-Abl), which confers resistance. In contrast, resistance develops in a

stepwise manner in the second cell line (KBM7), without a strong, clear event. This probably indicates the slow induction of different resistance mechanisms that are selected for, so in the end the resistance is as high as in the first clone.

The six golden rules in intratumoural ADME

Cancer cells fight back against drug treatment because they are armed to survive. In a review I wrote several years ago (*Curr Cancer Drug Targets* 2009, 9:652–674), I proposed ‘six golden rules’ in intratumoural ADME:

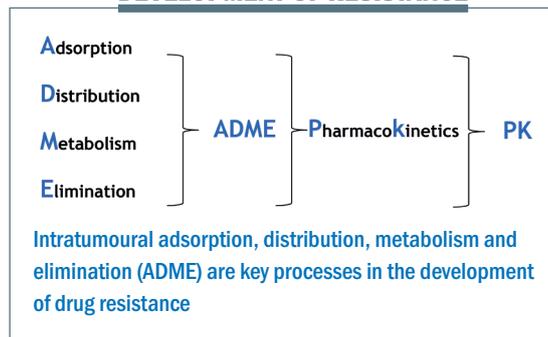
Rule 1: Pharmacokinetics in the blood are different from the intratumoural pharmacokinetics. An example would be two patients with the same plasma drug levels but very different drug levels in the tumour, so the patient with the lower intratumoural drug level will have a higher risk of cancer relapse.

Rule 2: There are three main systems involved in drug disposition in cancer cells (see figure opposite, top):

- influx of the drug into the cell (SLC channel)
- efflux of the drug out of the cell (ABC pumps)
- degradation of the drug by xenobiotic metabolising enzymes (XME).

A drug targeted to a cancer cell may enter through a channel in the membrane, using solute carriers (SLC). Efflux transporters such as

DEVELOPMENT OF RESISTANCE



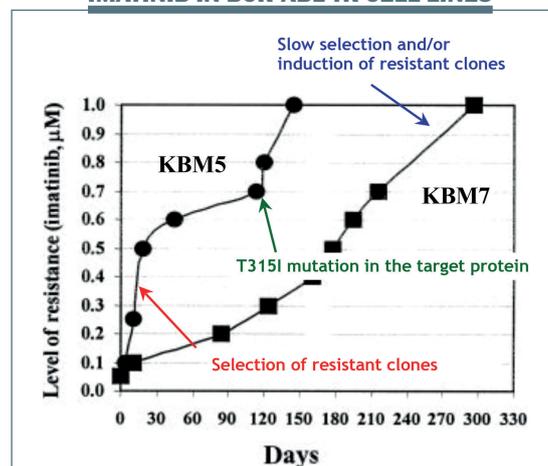
the ATP binding cassette (ABC family) may take the drug or its metabolites out of the cell. The drug may be degraded inside the cell by xenobiotic metabolising enzymes, typically cytochrome P450 enzymes (CYP). There is over ten times more endoplasmic reticulum (ER) membrane than cell membrane in tumour cells, providing a large volume for CYP metabolising enzymes.

Rule 3: There is synergistic interplay between these three systems – SLC, ABC and XME – that has been built over hundreds of millions of years of evolution. A drug can enter the cell, bind to the nuclear receptor and direct the DNA to increase the number of efflux pumps as well as CYP or other xenobiotic metabolising enzymes. The same receptor can increase both efflux and degradation enzymes inside a cell.

In a sensitive cancer cell, the drug enters the cancer cell and carries out its action that kills the cell. However, eventually the cell fights back by reducing influx and increasing efflux and CYP enzymes, so there is a much lower level of the drug (e.g. ten times less drug) inside the cell.

Rule 4: There is great variability in the expression of these three systems between tumours. This occurs because DNA is highly unstable in cancer cells, with high rates of

DEVELOPMENT OF RESISTANCE TO IMATINIB IN BCR-ABL TK CELL LINES



Different timelines for development of resistance indicate differences in the mechanisms of resistance operating in the two cell lines KBM5 and KBM7

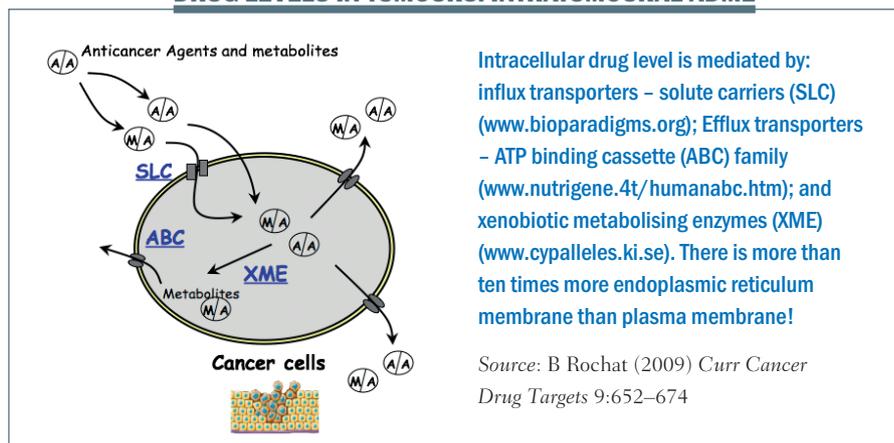
Source: B Scappini et al. (2004) *Cancer* 100: 1459–71, John Wiley and Sons

mutations and activation of transposons (mobile DNA sequences). Under the stress that an anti-cancer drug can impose on a cell, the transposons can activate different CYP enzymes to be overexpressed inside the cell (see, for instance, *Cancer Res* 2005, 65:3726–34). The figure below shows glucuronidation activity in normal colon biopsies (white bars) compared to that in cancer biopsies (grey bars), illustrating the difference in activity in different patients. The much higher enzyme activity in some patients explains why their intratumoural drug levels will be much lower than in those with lower glucuronidation activity. Similar variability – up to a ten-fold difference or more – is seen in influx and efflux proteins.

Rule 5: Intratumoural CYP can play a role in anticancer drug degradation and the synthesis of messengers involved in cell survival or proliferation. Certain CYP enzymes, such as CYP1A1, 1B1 and 2J2, are poorly expressed in the liver or intestine, but can be overexpressed in many tumours. CYP enzymes expressed in the liver are the ‘canonical’ enzymes and are studied extensively, especially by pharmaceutical companies. Those expressed in cancer cells are the ‘exotic’ enzymes, and are poorly studied. Many extrahepatic CYP enzymes are overexpressed in tumours, with the potential to affect intratumoural pharmacokinetics only.

Rule 6: The three systems – SLC, ABC and XME – are all involved in the appearance of

DRUG LEVELS IN TUMOURS: INTRATUMOURAL ADME



drug resistance. This was shown, for example, in a study of mice with two types of tumour – wild type with normal efflux activity, or null ABCG2 (BCRP) genotype with lowered efflux for topotecan. Resistance to the topotecan developed much faster in the wild type mice than in those with deletion of the ABCG2 transporter. The first conclusion was that each tumour was unique in its response to the therapy; the

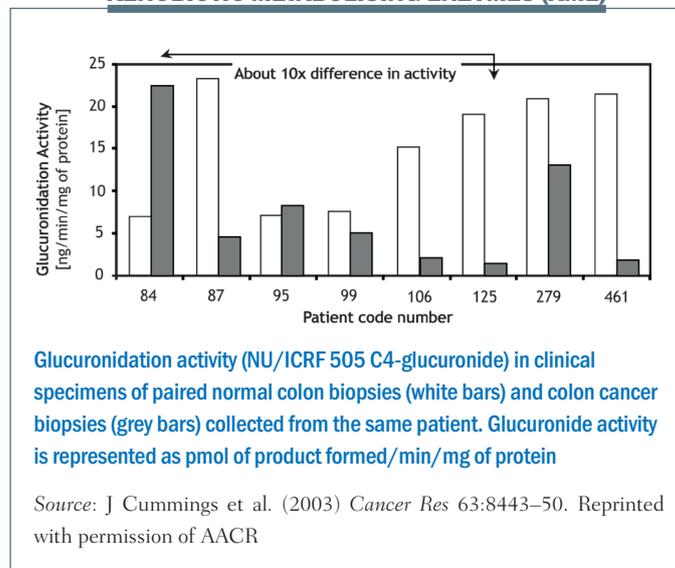
second conclusion was that efflux was involved in resistance, but this was a transient event (*PNAS* 2007, 104:12117–22; S Rottenberg, Biomedical Transporters conference 2007, Bern, Switzerland).

Why study intratumoural pharmacokinetics?

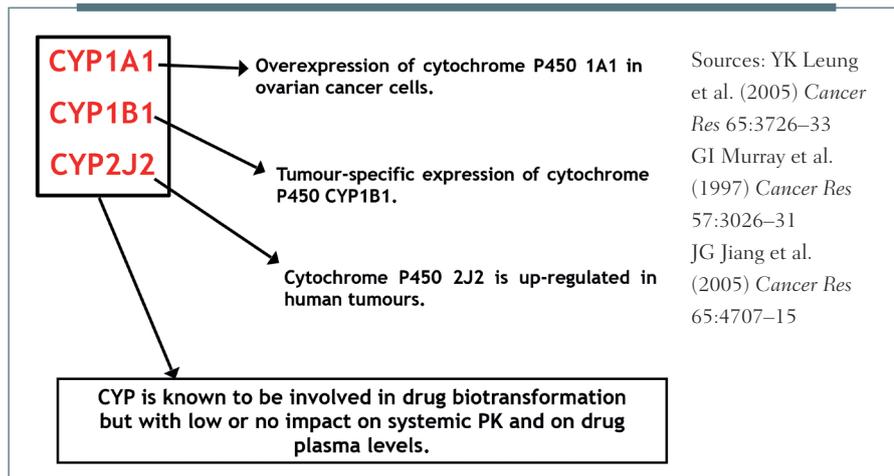
Pharmaceutical companies study the pharmacokinetics of cancer drugs, but focus on only one aspect – the metabolites produced by the liver and not by the cancer cells. We recently discovered more than 40 metabolites of tamoxifen circulating in the plasma of treated patients (*Anal Bioanal Chem* 2014, 406:2627–40). This example shows that it is important to remember that metabolising enzymes have strong efficacy in degrading drugs, but that their intratumoural role is generally ignored.

We recently studied the role of three extra-hepatic P450 enzymes – CYP1A1, 1B1 and 2J2 – which are

XENOBIOTIC METABOLISING ENZYMES (XME)



MAIN EXTRA-HEPATIC CYP ENZYMES OVEREXPRESSED IN TUMOURS



rapidly biotransform various TKIs (*PLoS One* 2014, doi:10.1371/journal.pone.0095532).

All of this suggests that CYP2J2 could be a good target enzyme to inhibit because it probably activates promoters of cancer cell growth as well as degrading TKIs. From a clinical perspective, there are already a few approved drugs known to be strong inhibitors of CYP2J2, including telmisartan, flunarizine, danazole and amiodarone. Using these drugs to inhibit CYP2J2 could provide a novel strategy to improve TKI efficacy and extend the time to relapse. It is similar to inhibiting beta-lactamase metabolising enzymes to increase drug exposure and reduce antibiotic resistance. I think this offers a promising approach for reducing the development of cancer drug resistance. ■

known to be overexpressed in many tumours – in the degradation of dasatinib, imatinib, nilotinib, sunitinib and sorafenib. Results showed that these three extra-hepatic CYP enzymes had strong affinity (Km) and degradation velocity (Vmax) for the five tyrosine kinase inhibitors (TKIs) tested. Degradation efficiencies were comparable to the major hepatic CYP, CYP3A4 (see figure above). We looked at the RNA expression of the enzymes in patients with renal cell carcinoma and hepatocellular carcinoma, in tumour biopsies as well as in their healthy tissue counterpart.

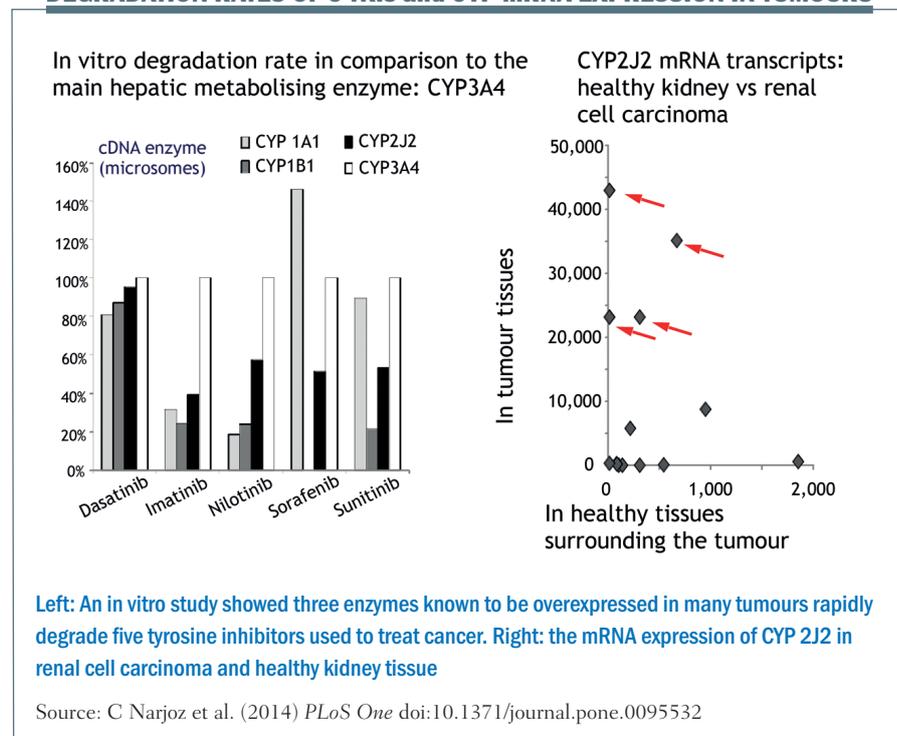
Results showed that CYP2J2 RNA was overexpressed in about one-third of the tumours, suggesting a probable high degradation of TKIs by CYP2J2 in these tumours.

What are the clinical consequences of intratumoural drug metabolism?

CYP2J2 is highly expressed in haematological cancers and promotes tumour cell growth, proliferation and metastasis. It is up-regulated in many human tumours, including breast, stomach, oesophagus, liver,

colon and lung (*J Pharmacol Exp Ther* 2011, 336:344–355; *Cancer Res* 2005, 65:4707–15, *Cancer* 2009, 28:93–96; *Life Sci* 2008, 83:339–345; *Cancer Res* 2007, 67:6665–74). CYP2J2 has been demonstrated to

DEGRADATION RATES OF 5 TKIs and CYP mRNA EXPRESSION IN TUMOURS





Daniel Helbling, of the Gastrointestinal Tumour Center in Zurich, Switzerland, hosted a live question and answer session



Q: Do you think the pharmacokinetic mechanisms of resistance that you covered are the mainstays of all resistance?

A: No, there are many different mechanisms by which cancer cells can develop drug resistance. But this is one mechanism we should think about, and consider inhibiting to increase intratumoural drug levels. It is similar to what happened 10 years ago when people worked on P-gp inhibition (ABCB1 efflux pump), with clinical trials using inhibitors of ABC transporters. Unfortunately, this turned out not to be possible because these inhibitors also affected healthy cells (e.g. in the liver or at the blood-brain barrier). This is different for CYP2J2, because it is expressed mainly in cancer cells, and only very poorly in healthy liver cells.

Q: Are there any case reports of adding CYP2J2 inhibitors to cancer treatments showing increased efficacy?

A: No. I think people have considered giving 2J2 inhibitors not as inhibitors of drug degradation but rather as inhibitors of messengers that are promoters of cell proliferation and metastasis. However, both mechanisms could potentially be targeted with the same inhibitors. This is ongoing, I believe.

Q: Is there any way to predict intratumoural pharmacokinetics?

A: It is a good question, and we should be able to do this. I tried to contact people in Geneva where they have computer models using kinetic parameters such as affinity of the enzymes for the drug and different compartments to simulate the pharmacokinetics in the whole body, in the plasma and in the tumour. The software is not designed

for modelling pharmacokinetics in tumours, but I think it should be possible, and the group wants to try it.

Q: Does radiotherapy influence intratumoural pharmacokinetics?

A: As far as I know radiotherapy kills cells so there will be no pharmacokinetics or degradation capability in dead cells. The other question would be whether radiotherapy activates transposons and maybe modifies DNA stability. I do not think that radiotherapy would be a feasible approach to modifying intratumoural pharmacokinetics. It is difficult to look at what is happening in the tumour, especially in a human, although it may be possible with an animal model. It has been looked at in the opposite way, using gene therapy for the CYP involved in activation of the pro-drug in the tumour (e.g. the alkylating agent cyclophosphamide), with the aim of using a lower dose of drug to reduce side-effects or increase intratumoural drug levels. This has been shown to be effective and promising in animal models.

Q: Do we know the drugs that are affected or prone to being metabolised by CYP2J2 enzymes?

A: There are only a few drugs that are considered to be substrates of CYP2J2. Why? Because in the liver the level of this enzyme is very low, and other CYP enzymes are involved in drug metabolism. There are a couple of drugs that are not biotransformed by usual hepatic CYP enzymes, including 3A4 and 1A2, but are biotransformed by CYP2J2 (weakly expressed in the intestine). In vitro experiments show that CYP2J2 is able to degrade a lot of drugs, but,

of course, this is not in the liver. However, where it is expressed, such as in many tumour tissues, it can be a strong enzyme in drug degradation.

Q: Which anticancer drugs that we use every day would be most prone to have a better efficiency by giving a CYP2J2 inhibitor?

A: According to our results, with almost all of the TKIs we tested, CYP2J2 is as efficient, or very close to being as efficient, as 3A4, which is the most important enzyme in the liver in terms of degradation of drugs. Expression of 2J2 depends on the tumour. In a prospective study, we looked at CYP2J2 overexpression in 14 tumour biopsies and their healthy counterparts. One-third showed a very high CYP2J2 expression, which was compatible with high intratumoural drug degradation. If the enzyme is present then you could expect that most TKIs would be rapidly degraded, specifically in the tumour.

Q: Would this pave the way for clinical studies?

A: I think and hope so. Some caution would be needed because CYP2J2 is expressed in the heart, so you would not want patients to be to highly exposed to an inhibitor for an enzyme that plays a role in the heart. However, several drugs that are inhibitors of this enzyme are already on the market (telmisartan, flunarizine, danazol and amiodarone), and are used in patients for chronic treatment, with an acceptable safety profile.

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REVIEWS

CLINICAL
ONCOLOGY

Gazing at the crystal ball of European radiotherapy

JENS OVERGAARD

Although radiotherapy is a key component of cancer treatment, provision of this modality is not immune to limits placed on health-care expenditure. Recent studies suggest European radiation oncology resources will generally be insufficient to meet future, and in some cases current, needs. This challenge and how it might be addressed is discussed here.

This article was first published in *Nature Reviews Clinical Oncology* vol. 12, no. 1, and is republished with permission © 2015 Nature Publishing Group. doi:10.1038/nrclinonc.2014.205

The silver tsunami is coming: the post-World-War-II baby boomers are reaching the prime age for cancer onset and the number of new cancer cases is expected to rise for many years to come.¹ Furthermore, the characteristics of the typical European patient with cancer are shifting from a reasonably fit person of around 60

years of age to a >70-year-old individual with one or two life-threatening comorbidities. The clinical management of all these diseases – particularly the cancers in question – demands huge resources with regard to the therapeutic armamentarium as well as the related health-care infrastructure and personnel. However, whereas the age group at

greatest risk of cancer is expanding rapidly, health funding is becoming increasingly limited and the numbers of healthcare professionals are mostly stagnating, thus resulting in a relative decrease in resources. In cancer care, this situation is probably most exaggerated in the discipline of radiation oncology: typically, 5% of all health expenditure is related to cancer treatment, and radiotherapy generally accounts for only about 5% of this expense. Although new systemic therapies can be extremely expensive, such treatments can be implemented easily and costs are limited to the treatment of individual patients. Radiotherapy, however, demands substantial infrastructure and, therefore, upfront investments; unfortunately the level of investment often lags behind the true need. This issue has been addressed in a number of recent studies, either considering the global situation and pinpointing the need for such infrastructure in developing countries with emerging economies,² or focus-

ing more specifically on the European scenario.³⁻⁶

The European situation has been clearly outlined by Datta and co-workers,³ who estimated considerable deficits in the current capacity of radiotherapy centres throughout the continent: the current numbers of teletherapy units, radiation oncologists, medical physicists, and radiotherapy technologists were 25.6%, 18.3%, 22.7%, and 10.6%, respectively, below guideline recommendations.³

This analysis was based on previous publications. Firstly, estimates and guidelines for radiotherapy infrastructure and staffing needs published by the European Society for Radiotherapy and Oncology (ESTRO) Quantification of Radiotherapy Infrastructure and Staffing Needs (QUARTS) group nearly a decade ago.⁷

Secondly, a report published in 2013 by the International Atomic Energy Agency (IAEA) on the European radiotherapeutic infrastructure⁸—although the validity of the data in this report has been questioned,⁹ the IAEA's overall conclusions probably are valid. When considering the requirements for 2020, the data presented by Datta et al.³ provide a dismal picture of the future availability of radiotherapy, and it becomes obvious that resource provision in most European countries, which is already far below the capacity needed today, will certainly become inadequate. This problem will be compounded over time, as an approximate 30% increase in new cancer cases is expected over



the next 20 years.¹ Optimised cancer therapy is multidisciplinary, and evidenced-based treatment decisions should be based on the availability of all relevant treatment modalities.

Nevertheless, approximately 50% of cancers are treated using radiotherapy, either alone or combined with other modalities.¹⁰ Moreover, the indications for radiotherapy are likely to expand further as this approach offers the ability to conserve organs and tissues, and because tumours are increasingly detected at an earlier stage or in patients in whom other therapies are contraindicated due to comorbidity.

The future of radiotherapy services is faced with three partly counteracting problems. Firstly, radiotherapy depends on advanced and expensive technologies, and in particular the development of computing power has enabled provision of more sophisticated and exact treatment. These technologies include the accompanying diagnostic facilities; precise imaging in real-time has become an important issue, and to some extent a bottleneck, in the development of precision radiotherapy. We must take advantage of these technical improvements and convert them into simple (semi)automatic procedures to facilitate treatment planning and delivery in the future. Presently, we might have a window of opportunity in which sufficient resources

are available to make such developments,^{4,5} before the tsunami catches up with us and necessitates the use of quick and 'one-size-fits-all' treatment setups. Urgent efforts to promote simplification and automation of dose planning and treatment delivery are needed in order to meet the future challenges.

Secondly, acute and late adverse effects are a major limitation of radiotherapy, and increasing awareness and greater insight into such complications are required. Exact knowledge of these toxic effects is lacking, especially regarding variation between individuals, which might enable modification of treatment based on genetic profiles related to radiosensitivity. In elderly patients, in particular, many adverse effects might also interact with different comorbidities (such as diabetes and cardiac problems).

This issue leads to the third challenge: the role of radiotherapy in the ever-changing treatment strategies for patient populations with varying epidemiological, demographic and clinical characteristics. The only way to establish the importance of such parameters is through large clinical trials that evaluate potential

therapeutic benefit in different patient cohorts, particularly patients who would currently be considered elderly, but will probably soon be considered as standard patients. Such trials should be performed in elderly patients with features characteristic of the age group in the general population, including relevant comorbidities. Our current guidelines are predominantly based on clinical trials with major exclusion param-

**“...the data ...
provide a dismal
picture of the
future availability
of radiotherapy...”**

eters, which provide data from ideal patients and, therefore, might not be generalisable to the future average standard demographic. Without representative clinical trials, which also should include studies evaluating the possibilities of avoiding or de-escalating treatment, we will be unable to adapt our technology rationally when resources become limited.

Analysing the data from the European overview,³ widespread geographical variation in radiotherapy resources is evident, and the more-detailed exploration in the ESTRO Health Economics in Radiation Oncology (HERO) studies⁴⁻⁶ more-precisely define the future needs and expenses linked with radiotherapy; however, that the current availability is far from sufficient is well known. Currently, resources seem most sufficient in Denmark, where tax-payer-funded health-care is provided free at the point of delivery, and radiation oncology is limited to five large regional and three smaller (satellite) departments at public hospitals.

This country has a long tradition of adopting evidence-based national treatment strategies. At the end of the last century it became apparent that the resources for radiotherapy were limited and a detailed evaluation of the national needs was provided by the professional societies in collaboration with the Danish national healthcare authorities. Denmark has the highest cancer incidence in Europe,¹ and therefore the Danish National Board of Health sought to address this challenge in the First National Cancer Plan in 2000, by recommending

“Urgent efforts to promote simplification and automation of dose planning and treatment delivery are needed...”

investment in upgrading the capacity for radiotherapy and imaging. In addition, national multidisciplinary cancer groups were formed to streamline cancer treatment and develop evidence-based national treatment guidelines, an approach that was implemented in response to the second National Cancer Plan of 2005. Subsequently, focus was placed on reducing waiting times, necessitating efforts to meet the recommended capacity of radiotherapy resources.

All this has led to the current situation, in which the resources are in balance with the needs, and hopefully will remain so in the future. The lesson that can be taken from the Danish approach is that careful planning based on the realistic estimated data for the national population, together with national evidence-based guidelines, and recording of patients and their outcomes in national clinical cancer databases, can result in improved cancer care. In Denmark, the overall resources linked with this approach have been reasonable, and the radiotherapy investment, in particular, is probably no higher than the expenditure on this modality in other countries.

There is no doubt that radiotherapy will continue to have a major role in the future multidisciplinary treatment of cancer in Europe, and that the required resources should be made available. Together with securing the necessary investment, we must focus our effort on identifying the indications for and streamlining of radiotherapy procedures, using a population-based platform and fac-

toring in the changing age demographics. If we do the work now, with the ESTRO–HERO project as an example,⁴⁻⁶ we can overcome the deficiencies of the past and meet the demands of the future.

Waiting too long will probably cause severe failures in the provision of cancer treatment that is likely to be required by a huge number of elderly patients in Europe by 2020. The problems we are facing in health and cancer care are enormous, and will not disappear if they are not challenged. ■

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newsround

Selected reports edited by Janet Fricker

Leisure time physical activity is inversely associated with CRC mortality

■ Journal of Clinical Oncology

For patients with colorectal cancer (CRC) leisure time physical activity (LTPA) both before and after diagnosis is inversely associated with all-cause mortality, an analysis of the National Institutes of Health (NIH) American Association of Retired Persons (AARP) Diet and Health study has found. The amount of TV watched both before and after diagnosis, the investigators showed, was associated with mortality.

Physical inactivity has been associated with higher mortality among survivors of CRC, but the independent effects of pre- versus post-diagnosis activity remain unclear. It is known that 55% of CRC survivors report watching more than three hours of TV per day, but whether TV viewing is associated with mortality among survivors of CRC has not been defined.

In the current study, Hannah Arem, from the National Cancer Institute, in Bethesda, Maryland, and colleagues analysed the associations of pre-diagnosis and post-diagnosis LTPA and TV viewing with overall and disease-specific mortality among patients with CRC. For the analysis the investigators used data from the NIH AARP Diet and Health study, which between 1995 and 1996 persuaded 566,398 AARP members, aged 50–71 years, residing in one of six US states or two metropolitan areas, to complete a baseline

questionnaire including sections on diet and lifestyle. Follow-up questionnaires on topics such as risk factors were mailed out periodically. Links were made between cohort members and state cancer registries. Participants reported LTPA hours per week using categories of never, rarely, <1, 1–3, 4–7, and >7 hours per week. TV viewing was assigned categories of 0, 0–2, 2–4, and >4 hours per day.

Of the 300,352 men and women considered at risk for CRC, 4,685 CRC patients were identified and 1,541 deaths occurred. When survivors of CRC reporting >7 h/wk of pre-diagnosis LTPA were compared with those reporting no LTPA, investigators found a 20% lower risk of all-cause mortality (HR=0.80; 95%CI 0.68–0.95; *P* for trend =0.021). When survivors of CRC reporting >7 h/wk of post-diagnosis LTPA were compared to those reporting none, they had a 31% lower risk of all-cause mortality (HR=0.69; 95%CI 0.49–0.98; *P* for trend =0.006), independent of pre-diagnosis activity. In comparison with subjects who watched 0–2 h/day TV before diagnosis, those reporting >5 h/day after diagnosis had a 22% increased all-cause mortality risk (HR=1.22; 95%CI 1.06–1.41; *P* trend =0.002), and more post-diagnosis TV watching was associated with a non-significant 25% increase in all-cause mortality risk (HR 1.25; 95%CI 0.93–1.67; *P* for trend = 0.126).

"Because surveys of survivors of CRC have shown a high prevalence of physical inactivity and TV viewing, these findings present an opportunity for clinicians to encourage behavioral changes to positively impact longevity," write the authors.

Putative biological mechanisms to explain associations between sedentary time, physical activity, and mortality, they add, include physical activity increasing insulin sensitivity and higher circulating insulin and insulin-like growth factors being associated with angiogenesis, tumour growth and anti-apoptotic activity.

■ H Arem, R Pfeiffer, E Engels et al. Pre- and post diagnosis physical activity, television viewing, and mortality among patients with colorectal cancer in the National Institutes of Health–AARP Diet and Health Study. *JCO* 2014 doi:10.1200/JCO.2014.58.1355

Physicians reluctant to follow studies recommending withholding treatment

■ Cancer

Despite the publication of a randomised phase III trial supporting omission of adjuvant radiotherapy in elderly women with early-stage breast cancer treated with lumpectomy and adjuvant therapy, nearly two-thirds of this group of patients continue to receive radiotherapy.

In 2004 the Cancer and Leukemia Group B (CALGB) 9343 trial established lumpectomy and adjuvant therapy with tamoxifen alone rather than both radiotherapy and tamoxifen was a 'reasonable' treatment for women older

than 70 years with stage 1 oestrogen receptor-positive breast cancer. The study showed a five-year local recurrence rate of 1% in the group receiving adjuvant tamoxifen plus radiotherapy compared to 4% in the group receiving tamoxifen only following breast conserving surgery. Omission of radiotherapy, however, has not been widely adopted into clinical practice. A publication evaluating a Medicare database of 13,000 women showed minimal changes in clinical practice following publication of the CALGB 9343 trial.

In the current study, Manisha Palta and colleagues, from Duke University in North Carolina, set out to look beyond Medicare to a SEER database based on geographic regions representing 28% of the US population. "SEER data are likely representative of national practices and not biased by the philosophies of particular academic institutions," write the authors. For the study involving 40,583 women older than 70 years with T1N0 hormone receptor-positive breast cancers, receipt of adjuvant radiotherapy after breast-conserving surgery was compared between those receiving treatment in the period 2000 through 2004 (before publication of the CALGB 9343 trial) and those receiving treatment in the period 2005 through 2009 (after publication).

Results showed that 68.6% of patients ($n=12,881$) treated in the earlier time period received some form of adjuvant radiotherapy compared with 61.7% ($n=13,440$) treated later ($P<0.001$). Additionally implant radiotherapy was used for 1.4% of the population in the earlier time period compared with 6.2% treated later ($P<0.001$). Results analysed by age group demonstrated that radiotherapy was administered less frequently to older women, with approximately 30% of patients aged over 85 years receiving adjuvant radiotherapy compared with more than 75% of those aged 70–74 years.

An earlier assessment of the impact of tamoxifen administration within the National Comprehensive Cancer Network institutions, by contrast, demonstrated that after publication of randomised trials, use of tamoxifen

increased from 24% to 45%. "Evidence suggests that the medical community may react differently to withholding treatment compared with adding a new treatment," write the authors.

One possibility, they suggest, is that financial incentives, either on behalf of the health system or practitioners, may contribute to the difference, with physicians incentivised to favour treatment over no treatment, particularly when either option is considered appropriate.

Use of patient decision aids for older women considering adjuvant radiotherapy after lumpectomy, add the authors, would be beneficial to enhance patient knowledge and allow them to be better informed about treatment options.

■ M Palta, P Palta, N Bhavsar et al. The use of adjuvant radiotherapy in elderly patients with early-stage breast cancer: changes in practice patterns after publication of Cancer and Leukemia Group B 9343. *Cancer* January 2015, 15:121:188–193

Nearly half a million cancers a year worldwide attributed to obesity

■ **Lancet Oncology**

Worldwide nearly half a million new cases of adult cancer in 2012 could be attributable to high body mass index (BMI), found a population-based study by the WHO's International Agency for Research on Cancer (IARC). The proportion of cases was greater among women than men and in highly developed versus less developed countries.

Recent statistics have shown that 35% of adults worldwide aged 20 years and older are overweight (BMI ≥ 25 kg/m²), including 12% classified as obese (BMI ≥ 30 kg/m²). Studies have also confirmed associations between high BMI and risk of oesophageal adenocar-

cinoma and colon, rectal, kidney, pancreas, gallbladder (women only), postmenopausal breast, ovarian, and endometrial cancers.

In the current study Melina Arnold, from IARC, and colleagues, set out to estimate the global burden of cancer incidence in 2012 attributable to high BMI in 2002, acknowledging the 10-year time lag between exposure to high BMI and outcomes. BMI estimates from 2002 were taken from the Global Burden of Metabolic Risk Factors of Chronic Diseases Collaborating Group, while the GLOBOCAN 2012 database of cancer incidence and mortality for 184 countries was used to estimate the numbers of new cancer cases attributable to high BMI.

The investigators estimated that, in 2012, 481,000 (3.6%) of all new cancer cases in adults (aged 30 years and older after the 10-year lag period) could be attributed to high BMI. Population attributable fractions (PAFs) were 5.4% (345,000) for women versus 1.9% (136,000) for men. Post-menopausal breast, endometrial, and colon cancers accounted for almost three-quarters of the obesity-related cancer burden in women (almost 250,000 cases); while in men colon and kidney cancers accounted for more than two-thirds of all obesity-related cancer (nearly 90,000 cases).

In countries with a high human development index (HDI), around 8% of cancers in women and 3% in men were associated with excess bodyweight, compared with just 1.5% of cancers in women and about 0.3% of cancers in men in low HDI countries. In a 'counterfactual scenario', investigators calculated that if BMI had remained as recorded in 1982, 118,000 cases of high BMI-related cancers could have been averted.

"These findings emphasise the need for a global effort to abate the increasing numbers of people with high BMI. Assuming that the association between high BMI and cancer is causal, the continuation of current patterns of population weight gain will lead to continuing increases in the future burden of cancer," conclude the investigators.

In an accompanying commentary, Benjamin Cairns, from Oxford University, notes that "resources targeted at obesity must be balanced against those for other important causes of cancer, particularly infections and tobacco use, which are each associated with much larger proportions of cases."

■ M Arnold, N Pandeya, G Byrnes et al. Global burden of cancer attributable to high body-mass index in 2012: a population-based study. *Lancet Oncol* January 2015. 16: 36–46

■ B Cairns. Cancer and high body-mass index: global burden, global effort? *ibid* pp 3–4

Information provision should be adjusted to the individual patient

■ Cancer Nursing

Depressive and anxiety symptoms among cancer patients are associated with lower satisfaction with received patient information and perceived helpfulness of that information, finds a secondary analysis of several large population-based surveys of survivors of lymphoma, multiple myeloma and endometrial and colorectal cancers. Depressive symptoms, the Dutch investigators showed, were associated with less internet use.

Providing appropriate information can result in cancer patients experiencing a better sense of control over disease and health-related quality of life, and making informed treatment decisions. Many cancer patients, however, report dissatisfaction with information, resulting from healthcare professionals misunderstanding individual needs. Too much information, too little information, or too complex information may be supplied. Relationships between information provision and depression can be bidirectional: inappropriate information provision can make cancer patients feel more depressed and anxious; while in patients who are already depressed

and/or anxious, perception of information can be hindered.

In the study, Olga Husson and colleagues, from Tilburg University, the Netherlands, set out to investigate whether there were associations between anxiety and depressive symptoms in cancer survivors and satisfaction with information provision and internet use. For the study 4,446 survivors registered in the Eindhoven Cancer Registry, diagnosed with endometrial or colorectal cancer between 1998 and 2007 and lymphoma or multiple myeloma between 1999 and 2008, were sent questionnaires including the 25-item EORTC Quality of Life Group Information questionnaire and the Hospital Anxiety and Depression Scale questionnaire. In total 3,080 patients (69%) responded, who were then categorised into four groups: no anxious or depressive symptoms ($n=1513$), depressive symptoms only ($n=587$), anxiety symptoms only ($n=636$), and both anxiety and depressive symptoms ($n=344$).

Using multivariate logistic regression analyses, in comparison to cancer patients without depressive or anxiety symptoms, those with anxiety symptoms were 30% less likely to perceive information as helpful (OR 0.7; 95%CI 0.5–0.9; $P<0.05$); while those with depressive symptoms were 50% less likely (OR 0.5; 95%CI 0.4–0.7; $P<0.001$); and those with both were 60% less likely (OR 0.4; 95%CI 0.4–0.7; $P<0.001$). Additionally, having depressive symptoms was negatively associated with disease-related internet use (OR 0.69; 95%CI 0.5–0.9).

"The results may indicate that information provision is suboptimal, either because it is not adjusted to the mental health status of cancer patients or because it is unsatisfactory and thereby causing anxious and depressive symptoms among cancer patients," write the authors.

For better mental health, greater attention should be paid to optimally adjust information provision to the individual patient and to check their understanding. "It is necessary to regularly check what

the patient has understood and whether the information was helpful. When necessary, the HCP [healthcare professional] must repeat the information several times, both between and within consultations."

Future studies, they add, should investigate on which subjects cancer patients want more or less information.

■ N Beekers, O Husson, F Mols et al. Symptoms of anxiety and depression are associated with satisfaction with information provision and internet use among 3080 cancer survivors. *Cancer Nursing* published online 14 September 2015, doi:10.1097/NCC.000000000000184

Comorbidities are a key driver in chemotherapy modification

■ British Journal of Cancer

Many older patients did not complete chemotherapy courses as planned, due to low-grade toxicities, a UK observational cohort study has found. Treatment modification and discontinuation for low-grade toxicity occurred more often among those with multiple comorbidities.

Delivering chemotherapy to older people can be challenging for clinicians, who need to evaluate which patients are robust enough to tolerate chemotherapy and/or continue treatment without modifications. The lack of older people in clinical trials has made it harder to make evidence-based decisions around management of chemotherapy in such patients. There are often concerns of increased risk of toxicity in older patients, with some studies indicating increased toxicity with age. Many studies, however, did not control for comorbidities, which may equally affect tolerance to chemotherapy, raising concerns that comorbidity rather than age is the contributing risk factor.

In the current study Tania Kalsi and

colleagues, from Guys & St Thomas' NHS Foundation Trust, London, set out to investigate which level of toxicity triggers treatment modification and early discontinuation of chemotherapy in older patients. Between October 2010 and July 2012, 108 patients aged 65 to 86 years (median age 72 years) were recruited from the oncology and chemotherapy clinic lists. Chemotherapy was palliative in 59.3% of them (64/108) and curative/neoadjuvant/adjuvant in 40.7% (44/108), with 47 different chemotherapy regimens administered, 16.7% of which involved concomitant radiotherapy.

Results showed that treatment modifications due to toxicity occurred in 60 patients (55.6%), of whom 35% (21/60) had no greater than grade 2 toxicity. Early treatment discontinuation because of toxicity occurred in 23 patients (21.3%), of whom 39.1% (9/23) had no greater than grade 2 toxicity. Treatment modification for low-grade toxicity occurred in 24.4% of patients with fewer than four comorbidities compared to 57.9% of patients with more than four comorbidities, while treatment discontinuation for low-grade toxicity occurred in 33.3% of patients with fewer than four comorbidities, compared to 50% of those with more than four comorbidities. The most common low-grade toxicity types resulting in treatment modification were fatigue ($n=8$), haematological ($n=8$), gastrointestinal ($n=6$) and infections ($n=5$).

"This study would thus support that treatment decision-making should not be driven by chronological age and that comorbid burden appears far more relevant," conclude the authors.

The findings, they add, have potentially significant clinical implications, including highlighting that the measure and reporting of lower-grade toxicity and its impact should be considered in the design of future clinical trials, especially low-grade fatigue and haematological toxicity. "This would better reflect real-life clinical decision-making and would assist clinicians in making evidence-based decisions regarding the risks of a par-

ticular chemotherapy," write the authors.

Further work, they add, is required to clarify whether low-grade toxicity has a greater clinical impact in older patients, or whether clinicians have a lower threshold for modifying/discontinuing treatment.

■ T Kalsi, G Babic-Illman, P Field et al. The impact of low-grade toxicity in older people with cancer undergoing chemotherapy. *Br J Cancer* 9 December 2014, 111: 2224–28

Spirolactone protects against anthracycline-induced cardiotoxicity

■ European Journal of Heart Failure

Spirolactone administered simultaneously with anthracycline chemotherapy protects both myocardial systolic and diastolic functions, a study by Turkish cardiologists has found.

Anthracyclines represent the cornerstone in treatment of numerous haematological and solid cancers; however, the side effect of cardiotoxicity can limit use and increase rates of mortality and morbidity. While the protective effects of beta-blockers, ACE inhibitors, and ARBs on anthracycline cardiotoxicity have already been demonstrated, the effect of aldosterone antagonism, which inhibits the last step of the renin-angiotensin-aldosterone system (RAAS), has been questioned. In the current study Mahmut Akpek and colleagues, from University School of Medicine, Kayseri, Turkey, set out to investigate whether spironolactone protects the heart against anthracycline-induced cardiotoxicity.

Between September 2011 and October 2012, 83 patients with breast cancer treated with anthracyclines were randomised to 25 mg/day spironolactone ($n=43$) or placebo ($n=40$), with administration commencing one week before the start of chemotherapy and ending three weeks after the end of the chemotherapy. The

choice of chemotherapy regimen was left to the discretion of the medical oncologist. For each patient, transthoracic echocardiography (TTE) was performed one week before the start of chemotherapy and three weeks after the end of chemotherapy, with patients also monitored for electrolyte imbalances every two to three weeks.

Results for the spironolactone group showed left ventricular ejection fraction (LVEF) decreased from 67.0 ± 6.1 to 65.7 ± 7.4 ($P=0.094$), while in the control group it decreased from 67.7 ± 6.3 to 53.6 ± 6.8 . The decrease in LVEF in the control group was significantly higher than that in the spironolactone group ($P<0.001$). For the control group there was a significant positive correlation between total dose of anthracycline and LVEF deterioration (epirubicin $r=0.655$, $P=0.001$; adriamycin $r=0.717$, $P=0.001$). For left ventricular end-systolic diameter (LVESD), the P -value for the interaction between the spironolactone and placebo groups was 0.001; while for left ventricular end diastolic diameter (LVEDD) the P -value was 0.002. In respect of cardiac biomarkers, the P -value for the interaction between the groups was 0.018 for creatine kinase MB levels, 0.006 for troponin I and 0.130 for NTproBNP.

The study, write the authors, has three major findings. First, spironolactone protects LV systolic functions against the adverse effects of anthracycline group chemotherapeutics (not only LVEF but also LV systolic and diastolic diameters were protected by spironolactone). Secondly, spironolactone showed an antioxidant effect against anthracycline-induced oxidative stress, and thirdly it protects the diastolic functional grade against anthracyclines. "Therefore, spironolactone can be a reliable treatment option in the protection against anthracycline-related cardiotoxicity," conclude the authors.

■ M Akpek, I Ozdogru, O Sahin et al. Protective effects of spironolactone against anthracycline-induced cardiomyopathy. *Eur J Heart Failure* January 2015, 17:81–89

Nurturing empathy an oncologist looks at medicine and himself

How do we allow such behaviour among colleagues? asks the author, after experiencing what it's like to feel vulnerable and pain when your doctor doesn't seem to care.

FAZLUR RAHMAN

Empathy in medicine matters. I should know – I have been a practising oncologist for 35 years. But it was only when, in a matter of seconds, I went from doctor to patient that I grasped its true significance.

A hiking trail that I had taken for granted for years betrayed me one day. The stones on a steep path that felt solid beneath my feet suddenly shifted, and I slipped hard, slid fast, and fell off a cliff. My right foot landed on a rock slab, crushing my right ankle badly, with five fractures.

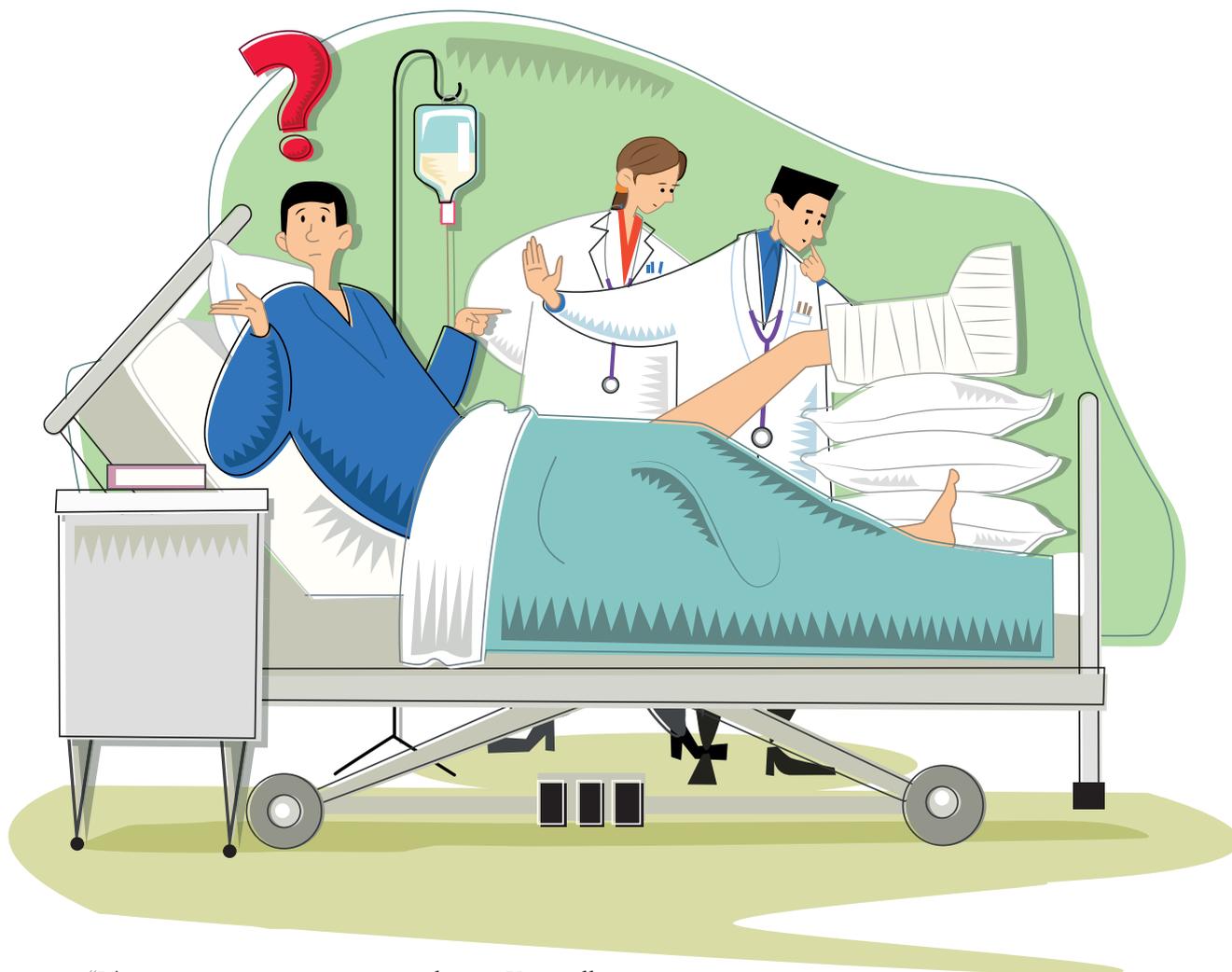
I was taken to the emergency room of the hospital where I worked. My orthopaedic colleague, Dr R, took me to surgery, but as a result of excessive and traumatic swelling of the joint, he could

not repair my ankle. He explained that cutting through the oedematous muscles and tissues would impede healing and increase the chance of infection. He was only able to temporarily stabilize my fractures using an external fixator, for which metal-alloy rods were drilled through my heel bone below and the shinbone above and then fastened together by bolts and screws. He explained that the definitive surgery would take place only after the swelling was gone. “The next operation won’t be easy, though,” he warned me, “so I am referring you to an ankle orthopaedist, Dr M,” who I knew practised in a large medical centre in a city far from ours.

Seeing my alarm, Dr R softened his tone. “Just try to put up with pain for a while,” he said.



This article was first published in *The Oncologist* vol. 19, no. 12, and is republished with permission. © 2014 AlphaMed Press doi:10.1634/theoncologist.2014-0387



“It’s not pancreatic cancer, you know. You will get better in time.”

I was not sure how to react to his words, which were meant to comfort me. It is true what he said – I was far luckier than any of my patients with pancreatic cancer, but that thought also brought some unpleasant memories of how some of my patients with pancreatic cancer had suffered. Would I suffer the same pain as my unfortunate patients, no matter how temporary? How capricious would my pain be? Doctors sometimes say things without thinking, and heaven knows how many times I may have said similar things myself in my own practice.

It was through my experience after sustaining this injury that I became aware of the behaviour of some clinicians – of some colleagues – that I still find incomprehensible. After their initial bursts of concern, they forgot to check on my

welfare. We could tolerate the incompetence of our colleagues (as long as it is feasible), yet when it comes to those who are handicapped, there is a certain lack of empathy. Psychiatrist Howard Shapiro put it best: “Handicapped doctors are treated like drug addicts,” he said. “Get them out of sight.”

Although it was not easy, I assiduously followed Dr R’s advice to reduce my swelling: diligent wound care and the constant elevation of my foot on four to six pillows day and night. My oedema subsided, but the hardware attached to my foot was taxing and painful. I had access to narcotics, but they made things worse. I found that the codeine combinations dulled my brain and caused nausea and abdominal bloating.

Ultimately, I saw that Dr M, the ankle orthopaedist, was my best chance of freedom and

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It was as if he had failed to notice that the joint was attached to a living being

rescue from the current situation, and I made the difficult trip to see him. As a fellow physician, I assumed he would surely empathise and understand my suffering.

To my shock, my belief and relief proved utterly wrong. He was unfeeling and appeared more interested in my fractures than in me. It was as if he had failed to notice that the joint was attached to a living being. He did not bother to touch me and was aloof with regard to the concerns I raised. I got the feeling that, to him, I was just a technical challenge and nothing more.

"I have looked at your x-rays and scans," he informed me, "and you have a hell of a lot of fractures." He then scheduled my surgery. I told him I was an oncologist, unsure if he was aware of my profession. "That won't change your surgery," he said.

After I settled in a hospital bed, a young doctor came to my bedside. "I am an orthopaedic resident assisting Dr M today," he said. He wanted to discuss one of my medications, an anticoagulant. "Why are you taking it?" he asked. "Did you have thrombophlebitis?" Then he was blunt: "Have you stopped it? We can't do surgery if you haven't. We can't risk haemorrhage on the operating table."

I was glad that he was careful about me before the operation. I assured him that I did not have thrombophlebitis and that my local orthopaedist gave me the drug in the hope of preventing it. I also told him that I had stopped it before coming in, as I was advised. Those were all the answers the young doctor was interested in, and he did not ask me any more questions about my health. He, too, didn't even touch me. I could see that the young doctor was copying his mentor, Dr M, well. The former's only concern seemed to be the anticoagulant that was noted in my record.

When the resident finished, a nurse gave me an injection. After that, I did not know what had happened until I woke up in the recovery room. I was confused at first and wondered why I was

in this strange place. Then I noticed a familiar face – it was Ara, my wife. "You have been in the recovery unit for six hours waiting to get a room on the floor," she said. "Surgery went fine." I reflexively looked at my right leg. It had a white cast, and the hardware was gone.

I realized that Ara had been sitting by my side all through this time except when I was on the operating table. I felt a pang of guilt. A vivacious, beautiful woman who looked elegant had become haggard, her eyes sunken, face dry. What had I done to her? Why had I gone for that cursed hike?

Finally, I got a room at midnight. By then I had begun to experience pain again, but this pain was of another kind, gnawing and oppressive. As the muscles and tissues of my operated ankle swelled more and more because of the cutting, they were compressed by the hard cast surrounding them. It felt worse than when I had the fixator, which at least provided room for the swelling to expand. I wanted to forestall the pain's ascending severity. I pressed the call button for the nurses to get an injection of morphine with an anti-nausea medication.

"Someone made a mistake in keying in your narcotics," a nurse said. "I have called for a reorder." Then there was more delay. "Only one pharmacist is on call at night," she informed me. "He is swamped, and dispensing morphine has stringent rules." She was genuinely sorry and offered me an oral codeine combination, which I accepted, but all it did was make me more miserable with nausea and abdominal bloating and little pain relief. Soon the pain got more severe, and I felt like a condemned prisoner without hope. By the time a nurse gave me a narcotic injection, it was at about 3 a.m. – three hours after my request.

Following the injection of morphine, I became peaceful and went to sleep. I wished I had stayed that way, but I was startled awake at 6 a.m., after Dr M came in for his morning rounds. Without so much as a "good morning," he held up an X-ray

in front of me. "Here is a copy of your X-ray after surgery," he said and then went on to quickly describe what he had done. "I have put in two plates and 14 screws to align the bones and some bone grafts to fill the gaps."

My eyes were blurry from the light, and I was still hazy from anaesthesia, exhaustion, and narcotics. I could not take it all in at the time and only later understood what happened, with my wife's help. After he finished telling me what he had done, he hurried to leave my room. Holding the doorknob on his way out, he said, "You can go home this morning."

I hadn't even had a chance to tell him about my ordeals at night. Ara, concerned about my pain and debility, pleaded my case: "He is too sick to travel, and we live far away." Dr M did not appear moved by what she said and barely talked to her. "He can rest in a hotel as well as he can in the hospital," he replied. "I will check him in the office in two days."

"You can talk to the discharge planner," he added, as he walked off.

I later discovered that he had admitted me as an outpatient case, and I had already spent the required night. One might read this story and see how unfair this discharge was and that I had the right to complain about it; however, when you are sick, you are vulnerable, doctor or not. You sign all the forms a hospital puts in front of you because you have to, and this absolves the hospital of any questionable conduct.

I wish I could say that my experience was unique in patient care, but it's not. I think I would be correct in assuming that numerous patients would identify with me. Sadly, as I looked back at my practice, I saw that Dr M's behaviour is partially explained by the silence of our colleagues. After all, neither I nor the other physicians had ever reproached another who had fallen short on bedside compassion.

True, the advances in specialisation and technology are saving lives or improving the quality of our lives, as they did mine. And my doctor was technically accomplished. Still, empathy is an integral part of care. Lack of empathy obvi-

ously compounds the distress of the patients, but what is not obvious is that it can have corrosive effects on the doctor's mindset. Nine medical specialty groups have found that 45 procedures and tests currently performed by doctors have no demonstrable benefit or can be harmful to patients. Although some tests and treatments are done with good intentions, others, unfortunately, might be done for reasons that are less than altruistic.

I believe that an empathic physician would try very hard not to subject his or her patients to tests or treatments with little benefit for them.

If we are to preserve our voice in healthcare, we clinicians must re-engage with our patients

empathically while giving our best care possible. Otherwise, the public will become increasingly disenchanted. In time, they may put greater demands on us, demands that are less than empathetic to our complaints about medical practice.

Equally important, we must begin teaching our students and trainees medical humanities as early as we can. The humanities should not be optional but rather a standard part of the curriculum. I believe this is important because empathy can be nurtured. Ample stories in the literature illuminate the subject of medical education. An example is Anton Chekhov's classic short story "Ward no. 6," in which a doctor who was indifferent to the dehumanising treatments of his patients ends up, by quirk of fate, being a patient in his own hospital. He is horrified by the pain and indignities heaped on him, the same pain and indignities his patients suffered routinely for years under his watch. A terrible, agonising thought torments him: "How could it have happened that for more than twenty years he had not known it and had refused to know it?" Any medical student who is asked to contemplate this cannot help but get some sense of empathy for patients. ■

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