European School of Oncology
Learning to care

Cancerworld

Number 40, January-February 2011

Education & knowledge through people & facts

Klaus Meier

➜ Klaus Meier: together we can offer the best of both worlds ➜ The TV campaign that is giving hope to Romania's leukaemia patients ➜ Managing risk: cancer control in the BRCA era ➜ Compassion goes beyond empathy: the views of a pioneer in supportive care

Contents

Published by
European School of Oncology

Direttore responsabile
Alberto Costa

Registrazione Tribunale di Roma
Decreto n. 436 del 8.11.2004

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

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

Our role in moulding the image of cancer

Kathy Redmond ■ EDITOR

Breaking the taboo on cancer and bringing discussion of the disease and the stories of cancer patients into the public arena has to rank as one of the big achievements clocked up since Nixon declared a war on cancer in the early 1970s. Eleven years ago, the live broadcast of American TV presenter Katie Couric undergoing a colonoscopy showed how far society and the media had moved, and was a good example of the inventive use of media to promote awareness about prevention and early detection that could help save lives. Stories tracking our growing understanding of what cancer is and how best to treat it are gradually succeeding in supplanting traditional responses of panic and fear with a more rational approach that helps patients play an active role in their treatment. Human stories about how cancer affects the lives of patients and their families have helped break the social isolation of those living with cancer and confront discrimination.

That's the good news. The bad news is that, with the best will in the world, cancer can be a difficult subject to cover well – the mass media is not at its best when dealing with stories involving many uncertainties, and it often struggles to get across complex pictures of risk and risk management. So though the quantity of coverage has improved, especially with the proliferation of online information, there is a big question about quality. A study by researchers at North Carolina State University has shown that many online news stories about cancer may actually add to readers' confusion.

A recent opinion piece in the *New York Times* has highlighted another unsettling trend in the way breast cancer, in particular, is being 'marketed' by campaigns – be they advocacy groups or corporations doing their bit for the cause. Messages are often dominated by images of young women, with a highly sexualised focus on their breasts, and 'sassy' upbeat messages that may be designed to promote self-examination, but fail to get a serious message across to the right people. Somewhere along the line, the reality of breast cancer, which affects primarily older women, and presents real challenges in terms of body image, not to mention the possibility of dying of the disease, has got lost.

In fact, far from helping, these campaigns are probably undermining the cause they claim to support.

It is impossible to control the way that cancer is presented to the public; however, it is possible to challenge irresponsible campaigning and journalism, and to promote critical and helpful media coverage. One way ESO has sought to do this is through our Best Cancer Reporter Award, which has now added a new prize, specifically for campaigning journalism, which this year was awarded to a Romanian television journalist for a campaign to set up a stem cell donor registry (see Desperately seeking a bone marrow match, p34).

You too can play a role by nominating journalists for the 2011 Award. Further information about the Award and nomination process can be found by clicking on the media tab at www.cancerworld.org.

Klaus Meier:

together we can offer the best of both worlds

Marc Beishon

Patients need doctors who know everything about them and their disease, symptoms and comorbidities. But doctors cannot also know everything about every drug their patient may need, nor can they provide regular support and advice to help patients get the most from oral cancer therapies. A strong partnership with pharmacists is the answer, says the founder of Europe's oncology pharmacy society.

When we look at the ideal multidisciplinary team working with patients throughout their cancer journey we tend to focus on the front-line healthcare professionals – oncology physicians of course, plus pathologists, radiologists, nurses, psychologists and others vital to providing the best care. Some, such as cancer nurses, are still having to battle to have the importance of their role recognised, and to gain acceptance as part of the wider team. But there is another major group of professionals that has had to fight hard for recognition of their contribution, and which simply does not enter the minds of many people. That group is pharmacists.

As Klaus Meier, president of the European Society of Oncology Pharmacy (ESOP), says, there are big gains to be made by integrating pharmacists into the patient journey, by bringing their knowledge of drugs and drug interactions directly to bear at the bedside, and also forming close relationships with patients when they leave hospital, often with prescriptions for drug regimens that need to be closely adhered to. With the cancer burden expanding across an aging population and more treatments coming on stream, demand for oncology pharmacy services is expected to at least double over the next ten years and Meier is keen to outline the very specific perspective they can bring to the care of cancer patients.

"Pharmacists are primarily scientists and we bring evidence of what will happen in the majority of cases, whereas doctors are more interested in learning about each patient from direct experience and especially about those who don't respond in a typical way," says Meier. "When we work closely together with physicians we get the best of both worlds, of theory and practical points of view.

"That's why I've tried to replace the term 'multidisciplinary' with 'multiprofessional' in cancer, to reflect the true coming together of professions rather than mostly physicians who are in the same discipline, i.e. medicine."

This is a message that Meier took to the European

TOBIAS HASE

CanCer Organisation (ECCO) when he was elected as a board member in 2008, a 'landmark' event for oncology pharmacists, he believes, that was achieved relatively quickly – eight years from the date he and colleagues set up ESOP.

A key step for ESOP came in 2005 when it become an umbrella organisation for national oncology pharmacy societies, instead of just a group of individual members. "Now our membership has shot up from around 300 to about 2200 in 32 countries around Europe, and it may surprise people to see such a large number – ESMO [Europe's medical oncology society] has only about 4000 members, so we represent a substantial number of the European cancer community."

Given that oncology pharmacy is a relatively young discipline, this presence at ECCO level is testimony to pioneering work carried out by members at national level and championed by Meier and colleagues, with Meier himself playing a leading role in his home country, Germany, where his 'day job' is currently head of clinical pharmacy at a hospital in Soltau, a town in a rural area some 50 km south of Hamburg.

There are tens of thousands of pharmacists around Europe, of course, working in hospitals and in community settings such as independent pharmacies and large chain stores. But since the explosion in cytotoxic and supportive drugs for cancer, and now the development of many new agents, including increasing numbers that can be taken orally, the oncology pharmacy specialism has developed to the point where qualifications are available in some countries. Alongside are various research programmes that are investigating everything from the economic validations of drug costs, to patient information and counselling.

Some pharmacists, such as those at Stockholm's Karolinska hospital, also play a leading role in studying cytotoxic drugs, working with clinicians. Clinical research priorities for oncology pharmacists include the stability and compatibility of drug combinations,

pharmacokinetics/dynamics in drug dosing, evaluation of dose banding, and medical errors.

Although Meier has himself been a pioneer in oncology pharmacy, notably in setting up centralised facilities for cytotoxic drug delivery, he views his achievements as not so much scientific but organisational, especially in later years with the formation of not only ESOP, but also the Deutsche Gesellschaft für Onkologische Pharmazie (DGOP, the German Oncology Pharmacy Society) in 1995, the International Society of Oncology Pharmacy Practitioners, ISOPP, in 1995, and a growing number of publications, meetings and masterclasses that are spreading good practice and gaining more support for the speciality.

"I am particularly proud of the book that the German society produces for ESOP, *QuapoS* [Quality Standard for the Oncology Pharmacy Service], which is now in its fourth edition," says Meier. "It is the result of a series of conferences in Luxembourg we started in 2001 on the standardisation of oncology pharmacy, and of various workshops. Although the printed book is in English, and despite a lack of funds, we have also made it available on CD and at www.esop.eu in 22 languages, including Arabic."

TOBIAS HASE

Surprisingly perhaps, given pharmacists' connection with drugs, ESOP is fiercely independent of industry, though it has been willing to collaborate on specific projects, including a recent survey done in partnership with Novartis that looked at the role that European oncology pharmacists play in dispensing treatment and disseminating advice to patients with chronic myeloid leukaemia. "If it is a true partnership with industry then that's OK," says Meier, "but we don't want to sell our souls and our knowledge." This preference to eschew industry sponsorship does, however, make the European and national goals of ESOP and its member societies more of a challenge to achieve, he admits.

This staunch independence has been a characteristic of Meier throughout his career in pharmacy, where he has been at odds several times with clinical colleagues and with hospital management. He sees winning the arguments as essential to promoting the effectiveness of oncology pharmacy, and indeed clinical pharmacy in general.

Meier was a relative latecomer to healthcare. Having started out with a masters in theology and the aim of becoming a teacher, he later switched to pharmacy. He worked for a spell in community pharmacies – "I could have stayed there and run my own shop," he says, "but I wasn't motivated by the business side and wanted to support patients more directly, so I entered the hospital pharmacy system and gained a postgraduate clinical qualification in 1989."

That qualification can be gained in three years in Germany – Meier himself has taught modules in Hamburg for some time – and since 2001, clinical pharmacists can obtain a further qualification in oncology pharmacy, which takes two years. "That's been a success as we now have 300 qualified

"If it is a true partnership with industry then that's OK, but we don't want to sell our souls and our knowledge"

oncology pharmacists in Germany and we were the European leader," he says. "The US has a board-certified oncology pharmacist qualification (BCOP), but I feel ours is more rigorous as we ask pharmacists to defend cases in front of a panel, whereas it is done by multiple choice qustions in America."

The UK, he notes, is working on a similar formal accreditation for oncology pharmacy through the British Oncology Pharmacy Association (BOPA), which is also one of Europe's longest standing such societies. The US BCOP programme is also available to pharmacists outside America – Spain, for example, has adopted it for its oncology pharmacists.

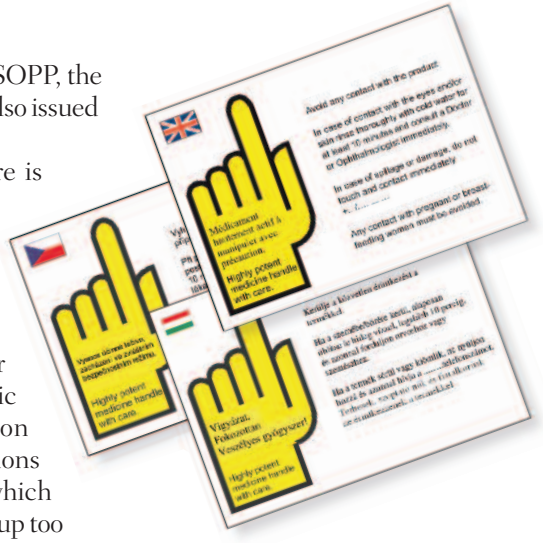
ESOP runs masterclasses and workshops to stimulate activity in smaller or less well-organised countries, particularly to encourage the take-up of postgraduate programmes. "We have also started a journal, the *European Journal of Oncology Pharmacy*, which includes reports from around Europe," he says.

It was while working at the Hamburg–Harburg hospital in the 1980s that Meier took himself out of the pharmacy to observe working practices of others and found that cytotoxic chemotherapies were being prepared by nurses with little attention to safe handling. "I also read a paper about a nurse who had lost her hair, and advice that people should not work with cytotoxic drugs for longer than five years – I thought why not four or six years? Looking further, I found several articles from the US where they had started central units for preparing oncology drugs, and thought we could do that in Germany."

Objections to setting up a central service for cytotoxic and cytostatic drugs came not only from doctors, who were concerned that pharmacists would be crossing over into their territory for decision making, but also from fellow pharmacists, who were worried about taking on the responsibility, says Meier. "But clearly from a safety perspective alone it has become vital that drugs that can be toxic to healthcare workers are prepared, transported and delivered as safely as possible, and the role of the pharmacy should be paramount," he adds.

The first quality standard edition published by the German society (DGOP) in 1996 focused mainly on conditions needed to comply with the delivery of cytotoxic drugs, notes Meier, and by the next edition in 2000 DGOP had started to certify pharmacies on the basis of the standard. Indeed, the current edition of *QuapoS* still majors on drug preparation and the role of a central pharmacy. ISOPP, the international society, finally also issued guidelines in 2007.

But Meier believes there is still a long way to go before uniformly high standards of safe preparation are achieved across European pharmacies – including eliminating as far as possible exposure to toxic compounds and medication errors, and ensuring infusions do not become unstable, which can happen if they are made up too far in advance.



Safety first. ESOP is promoting a 'yellow hand' label for cytotoxic drugs, to help ensure everyone who handles them is aware of the dangers and knows what to do in the event of a spillage

As a German colleague, Torsten Hoppe-Tichy in Heidelberg, reports in a paper, 'Current challenges in European oncology practice' (*J Oncol Pharm Pract* 16:9–18), although cytotoxic reconstitutions are under the control of pharmacy departments, in many hospitals other types of aseptic reconstitutions for infusions are still done at ward level, while a survey of pharmacists conducted by ISOPP and others showed best practice was not always followed even when respondents were aware of a rule. As part of its work raising awareness about the dangers of handling toxic treatments and disseminating knowledge about safe practices, ESOP has proposed a 'yellow hand' warning label for handling cytotoxic drugs with care, and what to do in the event of an accident.

"Of course we need safe conditions – we couldn't go on preparing cytotoxic treatments as we did 20 or more years ago, but there is much more that oncology pharmacists can bring to cancer," says Meier. "We have also been able to show hospital authorities that we can play a pivotal role in improving outcomes for patients, shortening hospital stays and reducing the drugs bill, among other benefits."

After success in establishing the central oncology pharmacy unit in Hamburg–Harburg in 1987, Meier worked on raising the profile of his and his colleagues' expertise within the hospital cancer team. As he notes, once pharmacists have dispensing and preparation authority for cancer drugs they should also assume responsibility, in partnership with the oncologist, for ensuring they are appropriate for the patient, and he is a strong advocate of the unit dose system. "This aims to deliver just the right

"We can play a key role in improving patient outcomes, shortening hospital stays and reducing the drugs bill"

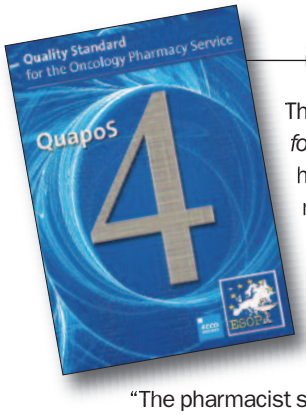
quantity of drug to the right patient in a way that minimises the work of nurses, who then have less to worry about when administering treatments."

Meier was one of the early innovators of unit dose systems, which are now widespread in hospital pharmacies for all types of drug, not just oncology, but are far from universal. By the time he had moved up to running a central pharmacy system for several hospitals in Hamburg, he had a service run from four locations serving 6000 beds and, in cancer, 40,000 treatments a year. "We were validating, for example, the three drugs in the FOLFOX colon cancer regime in 20 minutes and making deliveries of the first infusion to the hospitals in half an hour." That was a significant achievement because, as he explains, preparing a personalised dose has become more complex than just calculating the body surface area of a patient, while the logistics of managing a large patient chemotherapy population is certainly a major challenge in itself, as each treatment is usually prepared on the day of administration and means that patient appointments need to be linked as smoothly as possible with pharmacy resources.

Meier is not keen on the dose banding system, popular in countries such as the UK, which tries to cut costs and patient waiting times. Intravenous cytotoxic drugs are calculated on an individualised basis that are within defined ranges, or bands, and are rounded up or down to predetermined standard doses, which are delivered to the patient using syringes or infusions pre-filled to that standard dose. "I'm against dose banding as it should be possible to run a process that reflects each patient's situation," he says, noting, however, that he's heard from a colleague in Manchester, UK, that a pharmacy there has to cope with very different patient numbers from day to day – which would make unit (individually tailored) dosing very difficult.

A unit dose approach is important, says Meier, because not only is there a very narrow margin between a dose that is too toxic and one that is insufficiently effective for most chemotherapies, but in the last decade or so many drug regimens have become more complex and much more is now known about drug interactions with treatments for conditions such as diabetes and heart disease, as well as with a growing range of supportive therapies.

For Meier, the direction is clear – oncology pharmacists must also be involved at the bedside to ensure that overall 'pharmaceutical care' is optimal for each patient. Pharmacists, he says, have a crucial role to play in monitoring actual doses of therapeutic drugs based on feedback from blood plasma readings – which is becoming increasingly used – and in managing the other drugs and nutrition of patients. They are also well placed to help with side-effects such as pain and fatigue, and to reduce patient anxiety by explaining how their drug treatment will progress and change. Evidence for the importance of pharmacists in reducing drug-related problems has been reviewed by a team at the University of Bonn, which is also pursuing its own studies on breast and



SETTING THE STANDARDS

The first edition of the ESOP publication *Quality Standard for the Oncology Pharmacy Service* focused heavily on safe handling of cytotoxic drugs. The current (fourth) edition reflects the way the role of oncology pharmacists has developed, with a substantial section on supportive therapy, including the management of nausea and vomiting, pain management, mucositis and diarrhoea. It also carries a section on nutritional advice and therapy and unconventional methods of cancer therapy: "The pharmacist should respect the patient's views regarding alternative medicines and take his opinions seriously. However, it is also the pharmacist's responsibility to stress the importance and safety of evidence-based medicine and to inform the patient of the risks involved when using alternative medicines." A 'work in progress' section on research and development shows the growing involvement of oncology pharmacists in research as well as practice.
The full document can be downloaded from the ESOP site, www.esop.eu, and is also available, as a download or on CD, in 22 languages.

TOBIAS HASE

colorectal cancer, and patients receiving oral chemotherapy (*Pharm World Sci* 30:161–168).

This is not about treading on the toes of medical oncologists, Meier adds. "They know a lot about the specific drugs they are using but they do not have the knowledge of a thousand or more drugs that a pharmacist has and the relationships between groups of drugs. If they did they'd be pharmacists themselves." Certainly though there is a need for more pharmacology training for oncologists, as Jaap Verweij, a medical oncologist who studies drug mechanisms, told *Cancer World* recently (May–June 2010).

The contribution that pharmacists can make starts early in the patient's cancer journey, right at admission to treatment. "In many cases a patient comes into hospital and someone has to find out about the drugs they are taking, and the pharmacy is then told – but specific drugs may not be available and this can take time to sort out. One step is for pharmacists to see patients on admission to review their medications, as we do in my current hospital, and we draw up a profile of their drug needs and assess possible interactions with chemotherapy and biological agents, where it may be best to stop taking certain drugs during the hospital stay." Interactions with other prescribed medicines and the many popular complementary substances are often overlooked by oncologists, adds Meier (see also *Cancer World* July–August 2010 for more on interactions).

As patients move around the care system, there is also a need for hospitals to network much more with community doctors to help streamline the types of drugs being taken, adds Meier. "A hospital pharmacist can find, for example, that a patient may be on

"Medical oncologists do not have the knowledge of a thousand or more drugs that a pharmacist has"

"How can we support people who may take oral drugs for years or even for life?"

two different brand-name alpha blockers prescribed by his cardiologist and urologist, and not know he is taking an overdose," he says.

Meanwhile, the need to keep costs down is giving rise to another increasingly important role for pharmacists – providing evidence on the cost-effectiveness of treatments, when questions arise over whether to switch to oral anti-emetic drugs, for instance, or not use certain antagonists for cases of delayed vomiting (one study from the US showed a $200,000 saving over one year in a hospital with the latter approach). Oncology pharmacists are also likely to be increasingly involved in the economic validation of cancer treatment drugs as the number expands and as healthcare systems demand better cost–benefit analysis.

Meier has himself published on superior outcomes from integrating oncology pharmacy in cancer care, noting that not only can hospital stays be shortened thanks to better drug management and relationships with patients, but "drug costs can be cut by up to 20%, with only a small increase of pharmacy personnel costs of around 3%–5%."

Particularly challenging, adds Meier, is how to handle the growth in oral cancer drugs that will be taken mostly in the community. "How can we support people who may take oral drugs for years or even for life? Yes, doctors may be taking a regular blood count, but what if the patient is not taking the drug properly in the weeks between tests? Managing drug adherence can really only be done by someone who gives drugs to patients and can talk to them more often about how they feel, and can make a call to the doctor if necessary. Community pharmacists are the obvious partners, but as yet in Germany they are not involved much in oncology."

Other countries, the UK in particular, have made strides recently in expanding the role of community pharmacists with programmes such as flu vaccinations, health checks and prescribing of some drugs such as those for erectile dysfunction. In the complex insurance system in Germany and other countries, Meier considers that giving some form of reimbursement for the education and support role of the pharmacist, and the partnership with physicians, could more than pay for itself when set against the problems often encountered with drugs that can cost thousands of euros a year – and that in any case all oncology prescriptions should be signed off jointly by physician and pharmacist in consultation with patients.

"It's like a study I've seen from Liverpool in the UK, where patients with depression had continuous support from local pharmacists, and 80% were better after six months. In Germany, we have 80% not better in six months." Expanding the role of community pharmacists, he adds, can also cut the number of people buying drugs on the Internet, once they realise that cheaper is not always better when the value of support becomes apparent.

"We also have to support people who will never comply with an oral drug regimen," he says, noting too that the many patients who receive conventional chemotherapy in ambulatory care also need education and support for issues such as side-effects and hygiene at home. The DGOP, he adds, started a nationwide campaign last year to raise awareness of the needs of cancer patients among community pharmacists in Germany, including topics such as supportive care for fatigue and other effects, and educational information that can be given to patients.

Initiatives by ESOP include drawing up standards and protocols in relation to administering prescriptions for oral anti-cancer drugs, for which simple leaflets are being created for each drug giving information about the three most common interactions and side-effects. Patients will also be urged to keep medication diaries and to seek counselling and advice from pharmacists.

"Again, we are not saying we are taking work away from other professionals, particularly hospital and community nurses, who do play a crucial part in supporting patients. But throughout our lives the only professionals who are always close at hand are community pharmacists and we are saying to nurses and

others that you can count on our speciality in drug education and delivery."

Clinical research is another area where oncology pharmacists are important, and Meier says that in Germany their contribution to ensuring trials are well conducted is recognised by industry. "Although we're not involved so much in early-phase trials where pharmacological action is critical, the involvement of pharmacists in phase III work, where we manage documentation and protocols, has been a big success as we help get better quality results. Doctors alone do make many mistakes in trials." However, pharmacists rarely get a mention for their role, he adds.

He was busy expanding the pharmacy system in Hamburg's hospitals until a private company took over and made big changes. "There are problems still when hospital managements see the pharmacy as only a cheap logistics operation for ordering and delivering drugs, and that's still the situation in many places, despite the evidence we are building up," he says. "In Hamburg they called into question our need to be close to the bedside."

Now running a pharmacy for two hospitals and 550 beds in Soltau, anyone looking for a model could usefully track Meier for a few days, observing ward rounds to talk to patients, the way prescriptions for chemotherapy are reviewed and indeed the use of a software package that Meier himself developed 20 years ago called Cypro, which his pharmacists use to check the protocol of prescriptions and validate and prepare them (the programme is now available commercially at www.cypro.eu).

He is certainly pleased that so much work done by DGOP has made its way onto the European stage. "ESOP now has a board of 14 people from around Europe, a growing number of work programmes, our own congress planned for Budapest in 2012, our journal, and targeted workshops," he says. Among the priorities are researching the effects of chemotherapy on health workers and developing collaboration within ECCO. "Now we're on the ECCO board, when our members run into conflicts with physicians we can tell them that we're all on the same side and we should push for more multiprofessional working, such as joining tumour board meetings."

More disappointing for him has been the international society, ISOPP, which he founded in Hamburg in 1996. "It has far fewer members than ESOP and hasn't developed country involvement as well as we have in Europe. I would like to push them to be more active, and I'd like to see them pay closer attention to the needs of all their members rather than, for instance, promoting particular devices at meetings that could cost more than the drugs themselves."

Personally, he has relatively little time to influence such matters now as he's four years from retirement, but with 'heavyweight' ESOP colleagues such as vice-president Alain Astier in Paris and secretary Per Hartvig Honoré in Copenhagen on board – both senior professors – there's little fear of momentum being lost. It's hard to see him taking a back seat when so much he's started is in train, though, but his wife and two daughters may have a say in this.

A clue comes in a comment about ESOP's membership – "I'm not satisfied that we only have 2200 members" – could he have an eye on overtaking ESMO's 4000?

Established in Prague in the year 2000, the European Society of Oncology Pharmacy now has 2200 members in 32 European countries and currently has a seat on the board of ECCO. Its *raison d'être* is summed up in the Ljubljana declaration of 2006:

"The close cooperation between oncology physicians and oncology pharmacists is vital for optimal patient care. The multidisciplinary approach will deliver best practice to patients within a clinical governance framework. Professional, close and timely collaboration will in particular ensure economic use of resources and improved patient safety."

For further information visit the ESOP website at www.esop.eu

"We should push for more multiprofessional working, such as joining tumour board meetings"

Management of metastatic pancreatic cancer: current strategies and future directions

Despite recent progress with combination regimens, pancreatic cancer remains one of the worst cancer diagnoses. Malcolm Moore reviews the current management of this disease and considers where progress may be made. Better biological understanding leading to more tailored treatments is essential, he argues, which means more phase I/II trials, and greater use of tissue sampling.

Pancreatic cancer is a significant cause of morbidity and mortality throughout the world. In Ontario, Canada, where I live and work, there are 1200 new cases and deaths each year in a population of about 12 million people. It is the fourth leading cause of cancer death in Canada, and is similarly an important cause of cancer deaths in many places around the world.

One of the challenges of treating pancreatic cancer, particularly in the use of aggressive chemotherapy, is the age distribution of those affected. As with many cancers, it has a high prevalence in the elderly. The average age of development of pancreatic cancer is over 70. Factoring the age distribution with the fact that the disease causes significant morbidity, we are dealing with a relatively frail patient population.

About 60% of patients with pancreatic cancer have metastatic disease at the time of diagnosis. The median survival in these patients is around six months. Approximately 25% of patients are diagnosed with disease

European School of Oncology
e-grandround

The European School of Oncology presents weekly e-grandrounds which offer participants the opportunity to discuss a range of cutting-edge issues with leading European experts in the field, from controversial areas and the latest scientific developments to challenging clinical cases. One of these is selected for publication in each issue of *Cancer World*.

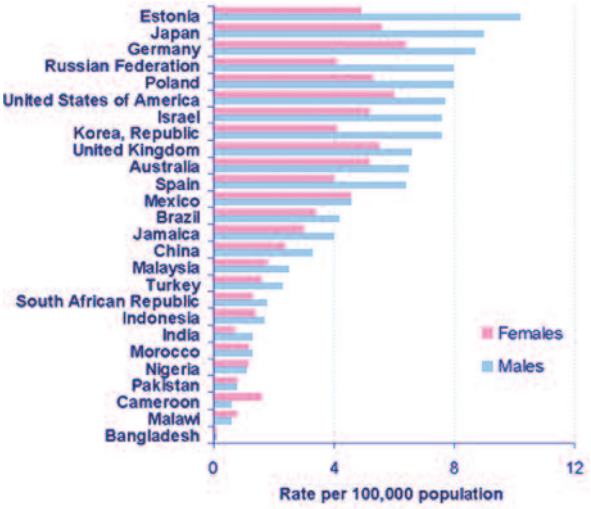
In this issue, Malcolm Moore, from the Princess Margaret Hospital, Toronto, Canada, reviews the management of metastatic pancreatic cancer, with reference to its epidemiology and biology. He considers the lessons learned so far and looks at the potential for targeted therapies and future directions for research. Jean-Luc Van Laethem, of the Erasme University Hospital, Brussels, Belgium, poses questions sent in by participants during the live webcast. The presentation is summarised by Susan Mayor.

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

that is localised but not resectable; we categorise these as locally advanced disease. Only about 15% of patients have resectable cancer. However, even where the cancers are resectable, median survival is still quite poor, at around 18 months, which is shorter than that of patients with metastatic colorectal cancer.

Putting all this together, 98% of patients diagnosed with pancreatic cancer will die from it within five years. To improve on this, we need better systemic therapy. Screening strategies are currently in very early stages and it is unlikely they will have a big impact within the next 10 years. We have therefore focused a lot of effort on effective systemic therapies.

MORTALITY FROM PANCREATIC CANCER



Age-standardised rates for 2002 in selected countries

Source: IARC. GLOBOCAN 2002. Cancer Incidence, Mortality and Prevalence Worldwide (2002 estimates)

New drug targets for pancreatic cancer

Pancreatic cancer is not like chronic myeloid leukaemia (CML) or gastrointestinal stromal tumour (GIST), where a single molecular abnormality drives most cases. It is a very complicated cancer genetically, with several genetic abnormalities. K-RAS is often considered the 'signature' mutation in pancreatic cancer, occurring in 75%–90% of cases, but there are abnormalities in many other pathways, including Hedgehog, aurora kinase, SMAD4 and p16. All of this factors into a rather complicated malignancy.

A very interesting study in which xenografts were created from 24 resected pancreatic cancers and the genome was sequenced showed the average number of genetic mutations was 63 (*Science* 321:1801–1806). These were clustered into 12 core signalling pathways, but there was marked heterogeneity in the pathways affected, with each individual showing a different profile of genetic changes – including deletions, amplifications and mutations – in these key pathways.

KEY MOLECULAR ABNORMALITIES

Oncogene	Relevance
K-RAS	Noted in 75% to 90% of cases
Sonic Hedgehog	Crucial role in embryological signalling
AURKA (aurora kinase)	Overamplification leads to chromosomal instability
Tumour Suppressor	**Relevance**
CDKN2A/p16	Normal function induces cell cycle arrest (with Rb)
SMAD4	Encodes transcription factor; lost in 50% of cases
p53	Role in cell cycle arrest and apoptosis
Also frequently will	**see abnormalities in genes involved with**
	Wnt/notch, JNK, integrin and TGF-B signalling.
	Apoptosis
	Cell adhesion
	Invasion

This heterogeneity suggests that if we are going to solve pancreatic cancer in the distant future, we are going to be looking at combination therapy and 'personalised' therapy based on individual profiles of these genetic changes.

Trials and tribulations of chemotherapy

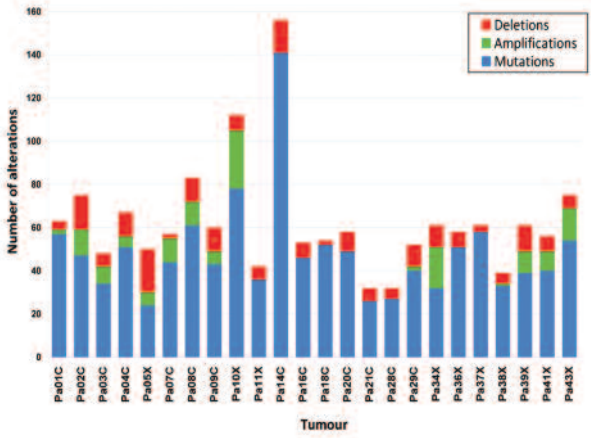
A study that I was involved in more than 10 years ago, in which gemcitabine was compared with 5-FU in metastatic pancreatic cancer, showed that, although all patients died of disease, those treated with gemcitabine had significantly better survival.

This study led to the approval of gemcitabine, the first drug approved for the treatment of pancreatic cancer. It was a relatively small study by current standards, with only 126 patients. Despite that, the results were clear, with a one-year survival of 18% with gemcitabine versus 2% with 5-FU, despite the fact that there was crossover.

Overall, the results demonstrate that gemcitabine has value in the treatment of pancreatic cancer. More patients treated with gemcitabine had stable disease and some improvements in quality of life and performance status. This was not generally associated with tumour response, which has been one of the traditional endpoints for drug trials.

Gemcitabine is now seen as a foundation for the modern treatment of pancreatic cancer. However, this study should not be interpreted as suggesting that 5-FU has no

NUMBER OF GENETIC CHANGES IN 24 PANCREATIC CANCERS



The individual biology of pancreatic cancer is very varied

Source: S Jones et al. (2008) *Science* 321:1801–1806, republished with permission from AAAS

activity. The dose and schedule of 5-FU used was probably not optimal, and it may well be that other doses have some value.

A number of relatively large phase III studies of gemcitabine with a second cytotoxic agent have been conducted in the subsequent 10 years. These include experimental drugs such as exatecan, and drugs approved for other conditions such as irinotecan, pemetrexed, capecitabine and oxaliplatin. While in some cases the phase II data showed promise, there was no improvement in survival when a secondary cytotoxic agent was added to gemcitabine.

These findings led to general pessimism about the possibility of achieving much of an improvement from combining multiple chemotherapy agents in the treatment of pancreatic cancer. However, analyses of these studies have suggested that patients with good performance status may obtain some benefit from combination chemotherapy.

Question: *Looking at the phase III studies, would you recommend a combination of gemcitabine plus a secondary cytotoxic agent, e.g. nab-paclitaxel, as an alternative to gemcitabine alone for treatment of pancreatic cancer in patients with good performance status?*
Answer: *That's an excellent question. Our practice over the last few years has been to use gemcitabine + cisplatin as an option for patients with good performance status (PS) who are interested in a more aggressive approach to treatment of their cancer, if we felt they could tolerate it. We have a community-based practice within a single healthcare system in Canada, so we see all of the patients in our centre. I would say that it is the minority of patients who could tolerate these more aggressive regimens. Anecdotally, we have had some patients who had good responses and seemed to do better.*

However, a gemcitabine + cisplatin study presented at ASCO in 2009 (Colucci et al, Abstract 4504) was a little disappointing. Not only did it fail to show a benefit, but there was no evidence of improvement even in the PS0-1 (good performance) population. This forces one to rethink whether the idea of giving more aggressive therapy to good PS patients is appropriate.

Question: *In your experience, are gemcitabine combinations well tolerated by pancreatic cancer patients?*
Answer: *We have a lot of experience with this combination, mainly because we were involved in a gemcitabine study in treatment of biliary tract cancer, which is fairly common in our area. I think tolerability really depends on the dose and schedule of gemcitabine. We found a lower dose, such as the Swiss regimen, was very well tolerated. With a higher dose, patients run into difficulty after three or four months.*

After the gemcitabine + cisplatin study presented at ASCO in 2009 showed disappointing results, many people became convinced that combination or aggressive chemotherapy probably had little role in pancreatic cancer. However, there are some data that suggest the opposite. The first is a study with gemcitabine + nab-paclitaxel (an albumin-bound paclitaxel). Paclitaxel, as far as we know, has very little efficacy against pancreatic cancer. However, the efficacy results in a phase II study conducted by Dan Von Hoff and

SURVIVAL IN RANDOMISED PHASE III TRIALS

	Gem	Gem + X	p value
Gem ± exatecan (Abou-Alfa, JCO 2006)	6.2	6.7	NS
Gem ± CPT-11 (Rocha-Lima, JCO 2006)	6.6	6.3	NS
Gem ± pemetrexed (Oettle, Ann Oncol 2006)	6.3	6.2	NS
Gem ± 5-FU bolus (Berlin, JCO 2002)	5.4	6.7	NS
Gem ± capecitabine (Herrmann, JCO 2007)	7.3	8.4	NS
Gem ± 5-FU/LV (Riess, JCO 2005)	6.2	5.9	NS
Gem ± capecitabine** (Cunningham, ECCO 2005)	6.0	7.4	NS
Gem ± cisplatin (Heinemann, JCO 2006)	6.0	7.5	NS
Gem ± oxaliplatin (Louvet, JCO 2005)	7.1	9.0	NS
Gem ± oxaliplatin (Poplin, ASCO 2006)	4.9	5.9	NS
Gem ± cisplatin (Colucci, ASCO 2009)	8.3	7.2	NS

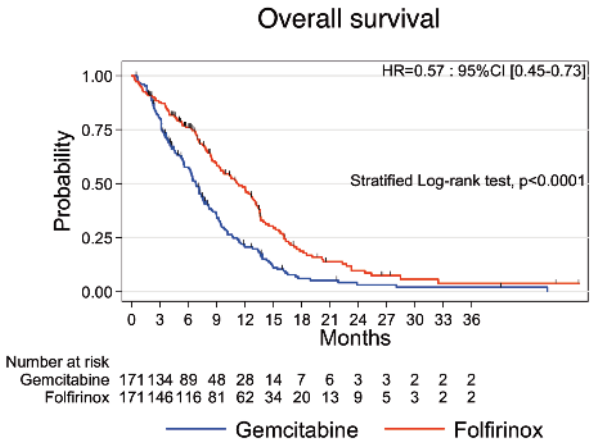
Attempts to improve outcomes from gemcitabine (Gem) by adding a second chemotherapy agent have not proved fruitful (figures indicate median overall survival, in months)

colleagues look quite encouraging (ASCO 2009, Abstract 4525). The median survival was nine months, compared to typically six months in metastatic disease. The response rate was 26% (2% complete response plus 24% partial response), as opposed to a typical response of 10% with gemcitabine. These are by no means definitive data, and it may be that these were highly selected patients. It is certainly an interesting enough result to warrant further studies, and a phase III study sponsored by Abraxis is currently ongoing.

The next study of interest was presented at ASCO three years ago by the CONKO group. It looked at the effects of a combination of oxaliplatin, 5-FU and leucovorin compared to 5-FU plus leucovorin in patients who had failed on gemcitabine, so this was a second-line population. The overall survival in the oxaliplatin–5-FU arm was 26 weeks, compared to 13 weeks in the 5-FU–leucovorin arm (Pelzer, ASCO 2008 Abstract 4508). This gives a significant improvement of three months. The study has not yet been published, but suggests that an oxaliplatin plus gemcitabine combination was not a wise choice, and combining oxaliplatin with 5-FU may be better.

A further study presented at ASCO (Reiss et al., ASCO 2009, Abstract 4006), randomised patients with advanced pancreatic cancer to systemic therapy with or without low-molecular-weight heparin. From our own experience, 25% of patients develop thromboembolic complications when they have pancreatic cancer, and many of those can be catastrophic. This study showed a significant reduction in serious thromboembolic events, but no improvement in overall survival. Having said that, the standard procedure with these patients is to use heparin, because survival tends to be short if patients have a thromboembolic problem. I think that this is something to review in the routine management of metastatic pancreatic cancer.

FOLFIRINOX VERSUS GEMCITABINE



Folfirinox (as a second-line treatment) showed a clear survival advantage over gemcitabine, but the toxicity of the combination regimen means it may not be suitable for all patients

Source: T Conroy et al. (2010) *JCO* 28:15s (abstract 4010), Published with permission

Is FOLFIRINOX the new standard of care?

This question comes out of the ACCORD11/0402 trial reported at ASCO 2010. The study has a fairly simple design and compares phase III folfirinox, which is 5-FU, leucovorin, irinotecan and oxaliplatin, with standard gemcitabine as first-line treatment for metastatic pancreatic cancer (Conroy et al., ASCO 2010, Abstract 4010).

The group had previously studied this regimen in a small group of patients (n=35) and had seen interesting activity in a good performance status population. On the basis of that, they opened a phase II/III study, and my understanding is that their intention was to go to phase III only if they saw a strong signal. They saw a 32% response rate to folfirinox and an 11% response to gemcitabine. Based on this, they continued to accrue patients into the study and expanded it as a larger phase III study. The patients who did well initially were included in the final analysis.

The regimen used was the folfox or folfiri regimen with the additional drug added in at full dose (folfox with full-dose irinotecan). This is an intensive and complex regimen, although we use folfox and folfiri very commonly in colorectal cancer and are very comfortable with these combinations.

As would be expected, the patients included were a selective population. They were young, with an average age of 61. All were of performance status 0 or 1 (almost 4% PS0 and 60% PS1), which is not the typical population for pancreatic cancer. It is important to note that the study included only good performance status patients, who could tolerate an intensive regimen.

The other unusual factor about the study population was that fewer than 40% of the tumours were in the pancreatic head, which is also not typical, as 60%–70% of cases are typically in the head. This occurred because the intention was to include

patients who had normal bilirubin, because of the drug regimen being used. Patients who had stents and did not achieve complete biliary drainage were not eligible.

In terms of adverse events, as expected there were major differences in the toxicity of the two arms. Neutropenia, febrile neutropenia, fatigue, diarrhoea and neuropathy all occurred more frequently with folfirinox. Almost half (42.5%) of patients on folfirinox also received G-CSF. Despite this difference in toxicity, the toxic death rate was low and fairly acceptable for this patient population.

The real crux of the study was a clinically and statistically significant difference in favour of folfirinox, with a partial response rate of 31% compared to 9.4% with gemcitabine, and a disease control rate of 70% versus 50%. Anecdotally, the data that were collected for gemcitabine were very typical for a patient population treated with this drug.

The median progression-free survival (PFS) values also favour folfirinox, with values of 6.4 versus 3.3 months (and highly significant *P*-values). Most importantly, the median and one-year survival values favour folfirinox: 11.1 versus 6.8 months for median survival and 48% versus 21% for one-year survival. The survival curves of the two arms demonstrate a clear separation (see opposite). We haven't seen this dramatic difference in survival with any other metastatic pancreatic study. Therefore, this is clearly an important result.

The real question and challenge for the community is: "Are there concerns about the trial methodology?" A very credible cooperative group conducted the study, and it is multicentred and randomised. There may be some concern about the fact that the patients on folfirinox generally got gemcitabine second line, while the patients on gemcitabine did not get folfirinox second line. Therefore, there is an imbalance. But while these are genuine concerns, the trial is certainly not fundamentally flawed.

Given that we've had so many negative studies of chemotherapy (this is the first one that is significantly positive), many may ask if we need a confirmatory trial to be sure it is appropriate to put patients through this very intensive regimen. There is no clear answer, but it is something that people are discussing. I think the big challenge that we will all face in our day-to-day clinical practice is that this is not a treatment for everyone. It will be difficult to distinguish between patients who are eligible for the more aggressive approach and those more suited to a palliative regimen such as gemcitabine.

The other issue, as a result of the data showing that oxaliplatin–5-FU is a successful regimen even in second-line patients, is whether it is really necessary to have all three drugs in the first-line regimen, and whether folfox with a second-line regimen would give the same results. This is, as yet, unknown.

At the end of the day, I think this is indeed a new standard for selective good performance status patients. However, most of us have not really used folfirinox in this patient population, so we will need to gain experience with it before general use in practice. There have been discussions in North America about whether we should do a phase II study of this with folfox, gemcitabine or nab-paclitaxel. This would allow us to get a sense of how patients improve and how this compares to other intensive regimens. I think this is going to be of great importance in the future.

Targeted therapy

Even with the recent folfirinox data showing improved survival, we are not going to do any better than that with more intensive chemotherapy. If we wish to improve survival beyond one year, we need to bring in targeted therapy.

Unfortunately, many of the studies so far have not been encouraging, including a study of putative RAS inhibitors with tipifarnib, a trial of gemcitabine versus the matrix metalloproteinase inhibitors marimastat and tanomastat, and a trial of EGFR antibodies with cetuximab.

The use of angiogenesis inhibitors has also been very disappointing in pancreatic cancer, with at least four negative phase III studies with different antivascular therapies including bevacizumab, axitinib and aflibercept. Sorafenib also has no efficacy. This may come back to the biology, as pancreatic cancer is not a vascular tumour, and I think there is no interest in taking these drugs any further in pancreatic cancer.

A study we did at the Canadian National Cancer Institute (NCIC) with erlotinib (an oral EGFR inhibitor) gave positive results (*JCO* 25:1960–1966), and this has now been approved for advanced metastatic pancreatic cancer. However, I think we still have some work to do on the molecular selection of appropriate patients.

This study had a simple design, randomising patients to gemcitabine plus erlotinib or placebo with no prior chemotherapy. The survival curve (see p 20) looks quite different from that for folfirinox. The median survival for the two groups was very similar because the curves come together at the end of the study. However, the overall hazard ratio was 0.81, which means a 23% improvement in average survival. The one-year survival increased from 17%

to 24% with erlotinib in this unselected patient population.

There are a couple of interesting observations from this study. First, patients who developed a rash with erlotinib had a significantly better outcome than those who did not. Patients who got a grade 2 rash had a median survival of 10.5 months and a one-year survival of 43%. Those results look very comparable to what you see with an intensive regimen such as folfirinox. The challenge has been to find out the biological significance of the data. Does it mean that everyone on the drug should have the dose escalated until they develop a rash in order to achieve a similar outcome? We do not know, and these studies are ongoing. However, the finding suggests that there is a population of patients within the overall group who do benefit.

We decided to find out whether there was a molecular method of identifying these patients. EGFR inhibitors work only in colorectal cancer patients with wild type K-RAS. Wild type K-RAS is not that common in pancreatic cancer, occurring in about 20% of cases. The hazard ratio for that population is 0.66, which shows a significant benefit with erlotinib. In the mutant population this value is 1.07, suggesting equivalence. This is an interesting observation, and further studies are being done to see if the benefit is confined to the wild type K-RAS population and is greater in this group.

Where do we go from here?

There are lots of interesting new targets that we can study in pancreatic cancer: Hedgehog pathway, Notch, heat shock protein and a number of other signalling pathways including AKT and MEK. There are drugs for most of these pathways, apart from K-RAS.

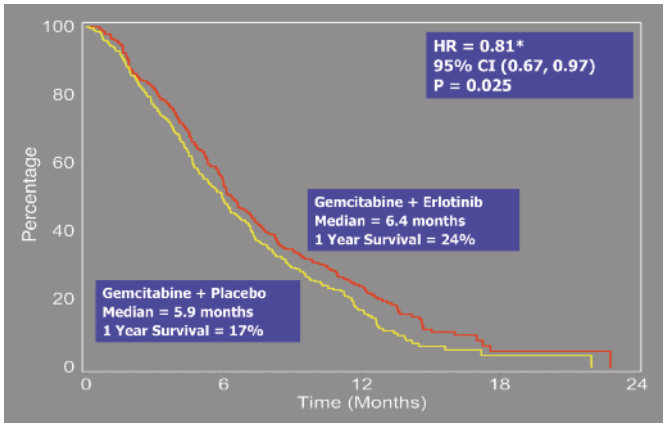
I think that it is important that we continue to look long term and realise that it is only by bringing in these types of drugs that we are going to make a major impact. The challenge over the next 10 years is to efficiently study a lot of different drugs and combinations to develop better therapy. In my opinion, we do need to focus primarily on the phase I and II arena. We also need to make sure we have uniform eligibility criteria. Trials should move on to phase III only when we get a strong signal – at least a two-month improvement in progression-free survival or survival, or a greater than 10% improvement in long-term disease control.

The other thing that we have not done so well in the past – and need to do better in future – is to incorporate biology into clinical research. It's not so bad having so many negative studies, but the issue is that we didn't collect tissue samples. If we had done this, we would know not only that the drugs were unhelpful, but also the reasons behind this. Therefore, we should be collecting tissue in all studies as a standard routine so we can try to understand what's going on at the biological level.

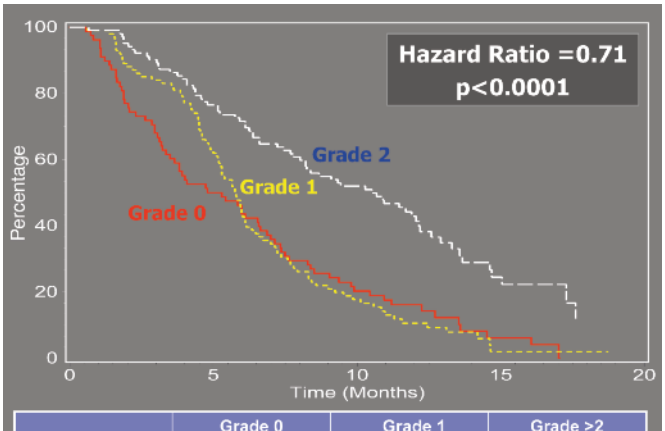
The other thing we have to start to think about is the heterogeneity of the

ERLOTINIB PLUS GEMCITABINE: OVERALL SURVIVAL

ALL PATIENTS



ACCORDING TO RASH SEVERITY

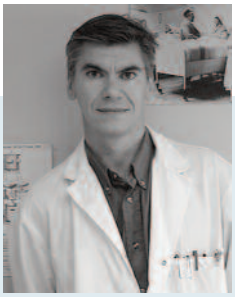


	Grade 0 N= 79	Grade 1 N= 108	Grade ≥2 N= 103
Median Survival	5.29	5.75	10.51
1 year Survival	16%	11%	43%

Adding the EGFR inhibitor erlotinib to standard therapy increased one-year survival from 17% to 24%; this figure rose to 43% for patients exhibiting a grade 2 rash

Source: MJ Moore et al. (2007) *JCO* 25:1960–1966. Published with permission

Jean-Luc Van Laethem, from Erasme University Hospital, Brussels, Belgium, hosted a question and answer session with Malcolm Moore.



Q: *Gemcitabine remains a good standard for the population, but we have to consider alternatives and possibly non-gemcitabine-based combinations, such as 5-FU–platinum in second line. We also need to find the best way to integrate folfirinox into our practice. One way to do that would be for future studies looking at gemcitabine as probably being a targeted therapy, with only about one-third of patients deriving real benefit. In the near future we may be able to select these patients based on the expression of gemcitabine nuclear transporters in tissue samples. This process is challenging in pancreatic cancer, as it is very difficult to get tumour samples. What is your feeling about targeted therapy? Do you think we should restrict erlotinib to only 20% of patients and should we rely on the chemo-evaluation? Should we make some effort to go further with this evaluation?*

A: Drawing from data in the NCIC study and my own experience, my opinion is that there is clearly a subset of patients that gets significant benefit from erlotinib – probably in the range of 10%–20%. Scientifically, it is attractive that this would be the K-RAS wild type group, because that fits with what we have learned in other diseases. However, I think the data that we generated on this in the NCIC trial is limited because we only collected tissue in about half of patients. At least two other confirmatory trials are looking at this specific question.

Anecdotally, I have a few patients in my practice who are still on erlotinib and are doing very well. We have tested them and they are all in the wild type group. Being able to identify patients who would benefit from treatment would be much more economically efficient.

Q: *What do you think about the need to overcome the RAS resistance via alternative pathways e.g. the MEK target? Do you think this process could be effective or should we investigate other pathways?*

A: We have never really had a proper RAS inhibitor. I think the next best solution would be to look at downstream pathways in RAS and target those, e.g. MEK and AKT. It is likely to involve more than one drug in order to do that effectively, because there is a lot of interaction between these pathways. If you turn off the pathway in one direction, there are other ways that the pathway can flow. Therefore, I think combination therapy is going to be the key to this problem.

Q: *Going back to systemic disease, should we consider adjuvant treatment even in resectable disease? The addition of folfirinox in this setting would be a good option to improve efficacy.*

A: I think that pancreatic cancer is clearly a systemic disease. Even among patients with resectable disease, almost all of them will recur. In many ways, we are probably asking too much of radiation therapy and if we had better systemic therapies, it is likely that we could have a more dramatic impact than with local therapy. There is no question that radiation can have an impact on a local tumour and prevent growth and progression. However, this will only be important if the overall disease can be controlled.

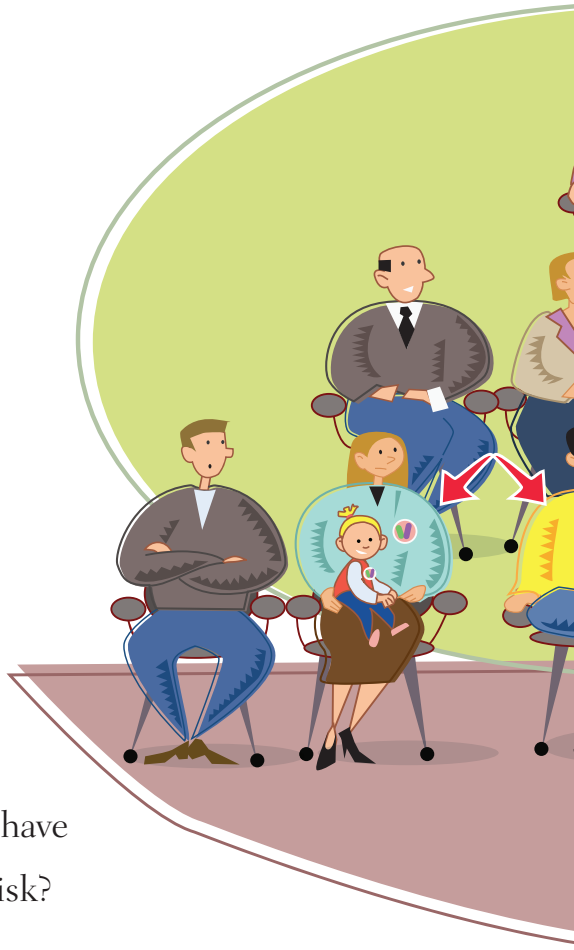
disease. Patients with different genetic profiles will need different approaches and we have to figure out how to incorporate this into our clinical trials. Pancreatic cancer is not a single-gene disease, and targeting single-gene pathways with single drugs is not going to be the way to make substantial progress. Therefore, we are going to have to work out how to screen multiple combinations of drugs in different patient populations. This is going to involve genetic profiling at the start of therapy.

Conclusions

It is easy to be pessimistic about metastatic pancreatic cancer, but we have made significant progress in systemic therapy. Over the past 10–15 years, one-year survival has improved from 2% to 25%. The folfirinox data show that good performance status patients can reach one-year survival rates in the range of 40%–50%. Using chemotherapy in the adjuvant setting has also improved survival and long-term disease control.

It is clear that there is a spectrum of patients, and 'one size does not fit all' in terms of treatment. Clinical judgement is important in choosing between the different therapies. However, even with new developments in treatment, pancreatic cancer is still one of the worst cancers with which to be diagnosed. We have a long way to go and need to find ways to look efficiently at all the interesting new compounds at the same time as developing the biological understanding of this cancer.

Promoting genetic literacy: cancer control in the BRCA era



Anna Wagstaff

As more is learned about inherited genetic mutations that make cancers more likely, there is an acute need to give those who live with the mutated genes clear information and accurate advice. But are health professionals equipped to look for signs of genetic predisposition, and do cancer services have the skills and expertise to help people manage their cancer risk?

The hereditary nature of some cancers has been known about for more than a century. Familial adenomatous polyposis, which inevitably develops into colorectal cancer if left untreated, was first described in 1859 with the first note of familial association in 1882. The first recorded operation for polyposis was performed by Lockhart-Mummery at St Mark's Hospital in London in 1918. By 1927 a registry for families with this syndrome opened at the same hospital, effectively establishing the first genetic cancer clinic, to keep a watch over those at high risk. By the 1940s, management of the condition moved towards prevention, as surgeons began to remove much of the affected bowel before the onset of cancer.

All cancers, by definition, involve gene mutations, the discovery of which has kept cancer researchers busy for decades, offering a stream of targets for the development of personalised therapies. In the case of genetic predisposition, however, the mutation is not just in the cancerous cells, but in the germline, meaning that it is carried in the DNA which forms part of a family's gene pool, and is passed down the generations.

The mutated gene may be 'high-penetrance', in which case carriers are very likely to develop the associated syndrome. In the case of the mutated *APC* gene associated with familial adenomatous polyposis, carriers are almost 100% certain to develop colorectal cancer by the age of 40 unless they act to lower their risk. Other inherited syndromes, however, such as the hereditary breast ovarian cancer syndrome linked to harmful mutations in the *BRCA1* and *BRCA2* genes, have a lower penetrance, meaning that carriers are much more likely than the general population of women to develop breast and ovarian (and other) cancers, yet they may remain free of cancer all their lives.

In the twenty years that have passed since scientists in Berkeley, California, identified the *BRCA* genes, a number of other germline mutations have been

identified that raise the carrier's risk of developing particular types of cancer (none as significantly as the *BRCA* mutations). The implications for the way society deals with cancer and professionals approach cancer control, are only now beginning to become clear.

Learning to live with BRCA

Francisca Bach Kolling from the Netherlands describes herself as one of the 'first generation' of identified carriers of a harmful *BRCA* mutation. Diagnosed and treated for breast cancer in 1990, aged 41, it was not for several years that she became aware of media reports about the discovery of a 'breast cancer gene'. Her

IN BRIEF

- Accounting for around 5%–10% of all breast cancers, harmful mutations in *BRCA1* or *BRCA2* increase a woman's chance of developing breast cancer over their lifetime by approximately five times compared to the normal population.
- Carriers of the harmful *BRCA1/2* mutations are also approximately 10–30 times more likely to develop ovarian cancer, with these mutations accounting for around 10% of all ovarian cancers.
- There is no single *BRCA* mutation, but a wide variety of mutations on these two genes, many of which have yet to be recorded. Only some have been demonstrated to be harmful.
- *BRCA* mutations can also raise the risk of other cancers, including gastric, pancreatic, colon and prostate cancer, as well as melanoma and male breast cancer.
- Other 'cancer genes' include mutated *APC* genes, responsible for familial adenomatous polyposis, which lead to colon cancer, and mutated *MLH1, MSH2 MSH6*, or *PMS2* genes, which are associated with hereditary non-polyposis colon cancer (HNPCC), a syndrome that also raises the risk of endometrial (uterine), stomach, ovarian, small bowel (intestinal), urinary tract, liver, and bile duct cancers.

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

Hereditary predisposition to cancer is something you live with for the whole of your life

mother had been diagnosed with breast cancer at the age of 53, so she decided to get herself tested, despite protestations from her GP that there was no reason to suspect a genetic predisposition. As it turned out, she did carry a variant of the *BRCA1* gene mutation – but her mother did not. It was her father who had passed on the mutation – a possibility that is frequently overlooked.

At her pre-test counselling she learned that some mutations that raise the familial risk of breast cancer also make ovarian cancer up to 60% more likely. "That hit me hard. It was like being told I had cancer again."

Francisca weighed her options. Already the mother of three children, she decided to have her ovaries removed, which greatly reduced her risk of ovarian cancer (for which there is no effective surveillance) and somewhat lowered her breast cancer risk. She underwent regular breast MRIs to maximise the chance that any new breast cancer would be picked up at a very early stage. This strategy paid off as nearly three years later she did develop breast cancer in the opposite breast. She opted for a full mastectomy, and nine years on seems to be in the clear.

Francisca has no major complaints about the quality of counselling she received, She does feel, however, that two important aspects of hereditary cancer continue to be overlooked by genetic cancer services. The first is that a hereditary predisposition to cancer is something you live with for the whole of your life. "You get the information and the counselling to help you decide whether you want surgery or not, but they don't then monitor how you are doing with it. How are you coping? Do you need support?"

The second is that your own genetic test result also has profound implications for all your blood relations. This information could save lives, but could also generate major stress and tension, burdening relatives with the knowledge of risk factors they would have preferred to have remained ignorant about. Francisca feels the onus of deciding who to tell what about the family *BRCA* mutation was left entirely on her shoulders, and she would have welcomed more help and advice from the genetics services, including practical ideas on how to go about this, advice about what kind of reactions to expect, and the chance to talk afterwards about how it went.

Her husband was immensely supportive, and together they organised a special weekend with the children, then aged between 16 and 22, to tell them the news. Their immediate response, says Francisca, was sympathy for her, but they also seemed quite relieved. "They had been expecting something worse – maybe that we were going to get divorced or something!" It was only later that the implications for their own lives really dawned on the children.

These are the 'second generation' – asymptomatic children, nephews and nieces of the 'first generation' – who are now growing up, forming relationships, starting families, in the knowledge that they may have inherited the gene mutation. This generation, says Francisca, is facing difficulties and dilemmas her generation never had to. While supporting other people with hereditary breast cancer, she has learned about the friction that can build up between siblings when it turns out that some are lucky and escaped the gene mutation, while others are not and have a lifelong worry for themselves and for any children.

It is often when this 'second generation' are themselves at the point of having children that the issue of testing comes to a head. One young man who knew he may have inherited a *BRCA* mutation told Francisca that he and his partner had decided to have children "in the normal way", without being tested. "They hope that if the children are girls, medical research will find some way to avoid them facing those difficult options of today; that there may be a pill or something to stop you getting cancer." An optimistic attitude, comments Francisca, who herself tends to favour double mastectomy for maximum protection, at least in later years – an option she says is very popular among 'hard-headed' Dutch women.

Young people who start new relationships struggle with the dilemma: 'When do I tell him/her?'

Another young man tested positive, and told her of the dilemma he faced in starting a family. He was thinking about trying to get a preconception genetic diagnosis, which involves screening an embryo *in vitro* before transferring it to the mother's uterus (a procedure available only in a few countries, and only where family history points to an exceptionally high risk). But he worried about what it would mean for his wife. "I am the carrier, we don't want to pass on the gene mutation to our children, but I have to ask my wife if she can take the burden, because it is quite a heavy procedure medically." Francisca herself wonders what she would have decided if she had known what she knows now when she was about to start her family.

The key, she says, is to find some sort of understanding and harmony with those you are living with. But relationships do not always last, in which case he or she may again face the responsibility of explaining about the mutation to a new partner, and trying to find way of living with that burden harmoniously. Francisca says that all young people in this position who start new relationships struggle with the dilemma: 'When do I tell him/her about my genetic predisposition?' "We have to give more attention to this group," she says, "because they are growing and they think about it quite differently to us."

Francisca is certainly trying to do her bit to help, by working with the Dutch Breast Cancer Organisation's advocacy group for hereditary breast/ovarian cancer, offering support and organising conferences. The group also campaigns to stop discrimination against mutation carriers, for instance by life insurance companies – an issue where they have scored some success. However, if you are a self-employed woman in the Netherlands, no-one will insure you against being unable to work if you know you carry the *BRCA* mutation.

RIGHTS AND REGULATIONS ACROSS EUROPE

The possibility of facing discrimination by employers, insurance companies, banks etc. can act as a serious deterrent to being tested for a genetic predisposition to cancer. Rights to privacy and duties of disclosure vary across the EU countries. The 154 page pamphlet: *Patients' rights, insurance and employment: A survey of regulations in the European Union* was published by the EU in 2002 (http://ec.europa.eu/research/biosociety/pdf/genetic_testing_eur20446.pdf), but this is now somewhat dated. A general protocol on genetic testing for health purposes was adopted by the Council of Europe in 2009 (see *Eur J Human Genet* 17:1374–1377).

A NEW FIELD IN CLINICAL ONCOLOGY

While the personal and social impact of greater knowledge and awareness of individual risk has been profound, the implications for cancer control and care may be no less radical. Bernardo Bonanni, head of the division of cancer prevention and genetics at the European Institute of Oncology (EIO) in Milan, talks in terms of "a small revolution" that has opened a new field in clinical oncology.

"We are increasingly looking at risk assessment as the first thing to do. We have many more tools now, including genetics, to study the individual risk of each patient or cohort of subjects. We have risk managers, experts in cancer risk, and we have to train new experts in this field."

He would like to see cancer services develop strategies based on models similar to those now widely used to identify and manage people at risk of heart attack or stroke.

Bonanni is at pains to challenge the popular misconception that risk levels are divided into 'standard' or 'high'. There is in fact no such thing as *'the BRCA* mutation'. Several mutations have been recorded on the *BRCA1* and *2* genes, some of them apparently harmless, while the harmful ones pose varying degrees of risk. Raised risks for various cancers can also be passed on through mutations in other genes, while other conditions such as metabolic syndrome, which raises androgen levels, or even a family predisposition to obesity, can also raise the risk of cancer. A point Bonanni likes to emphasise is that the majority of those who are referred to his High Risk Clinic belong to what he terms 'the grey zone' – they have a clear family predisposition to cancer, but the culpable gene mutation, or combination of mutations, will probably never be found.

What it all adds up to, he concludes, is that we are all on a spectrum of cancer risk, influenced by a myriad of genes in the family gene pool, interacting, of course, with our own particular environmental and lifestyle risk factors.

Understanding the risks, he argues, opens up new possibilities for refocusing cancer control away from treating established disease towards prevention and early detection. Six-monthly breast MRI scans from the age of 25 make no medical or economic sense in the general population, but make perfect sense if you can identify women with a demonstrable risk of developing breast cancer at such an early age. The cost and side-effects of chemopreventive agents such as tamoxifen are only outweighed by the advantages when used in women at high risk.

For this refocusing of cancer services to become reality, three things need to happen, says Bonanni.

Understanding the risks opens up new possibilities for prevention and early detection

- A network of multidisciplinary specialist clinics must be established, building on genetic clinics, but including oncologists, preventionists, geneticists, genetic counsellors, surgeons and other experts, who should discuss as a team the risk management plans for cases referred to them.
- The public, GPs, oncologists and other specialists need to become much more aware, to ensure that people understand their risk, get good advice on risk management, and are referred to specialist clinics as appropriate.
- A much greater focus is needed on developing and evaluating effective preventive strategies – a cancer equivalent of compounds already used as preventive agents, such as statins for heart disease.

Bonanni has been promoting all three. He argues for more and better teaching for oncologists and biologists to understand and practice risk assessment and risk reduction "exactly as cardiologists and internists do for their fields". In terms of service provision, he advocates for regional hubs of expert multidisciplinary risk management teams, working to agreed guidelines. His personal passion, however, is the development of preventive agents and strategies. He has been working for many years as part of a fairly small network of academic researchers who have swum against a tide of scepticism, but whose time may now be coming.

Bonanni's outlook is definitely closer to the young man hoping for 'a pill' than to Francisca and her generation in the Netherlands, who have largely opted for surgery. The reality is, however, that the evidence base for prevention is still very much work in progress, not least because proving that an intervention significantly reduces the risk of developing cancer takes more time and money and a bigger population study than proving treatment efficacy. "This is an ongoing field," says Bonanni. "We always share with people very clearly what is certain and what is uncertain so far. And this honesty is welcomed by them."

One area of growing certainty, says Bonanni, is the efficacy of regular breast MRI in picking up tumours in time to stop them spreading (*Cancer* 113:3116–3120; *JCO* 24:5091–5097; *J Natl Compr Can Net* 8:562–594), so long as this is done in expert centres, with up-to-date equipment and expert radiologists. In premenopausal patients, he adds, it is important that the MRI is done during the second week of the menstrual cycle, something radiologists don't always know.

Studies have demonstrated the value

When genetic testing goes bad

The importance of accessible expert genetic cancer services in the BRCA era has been highlighted by experience in the US, where private providers stand accused of mis-selling genetic testing to ill-informed medical professionals and individuals. Companies like Myriad, which was the first to clone the BRCA mutation, and whose claim to sole rights in the US to diagnose any BRCA mutation were largely invalidated by a US federal court judge last year, are charged with trying to circumvent cancer genetics clinics, pitching instead for referrals directly from GPs, most of whom do not really understand what they are dealing with. Equally worrying is the direct to consumer advertising – often with discounts offered if you can sign up other members of your family.

A recently published study conducted by the Yale Cancer Center (*Conn Med* 74:413–423), reported on a national US series of cases illustrating what can happen when cancer genetic testing is performed without counselling by a qualified provider. Three major patterns of bad outcomes emerged: wrong genetic test ordered; genetic test results misinterpreted; inadequate genetic counselling. The results, documented in the report, included:

- unnecessary prophylactic surgeries
- unnecessary testing
- psychosocial distress, and
- false reassurance resulting in inappropriate medical management.

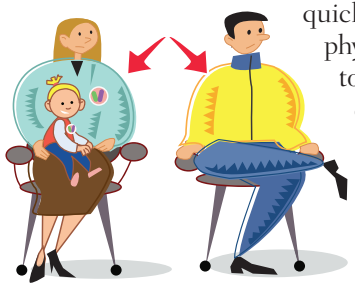
One family doctor consistently ticked the 'Jewish' box on the test form, thinking he was doing his patients a favour as it is easier to claim the costs for the *BRCA* test on insurance if you are Jewish. What he didn't realise is that there is a particular 'Jewish' *BRCA* mutation, and this was the only mutation that his patients were tested for.

of the selective oestrogen receptor modulators (SERMs) tamoxifen and raloxifene in risk reduction for ER+ breast cancers. The IBIS II study is investigating whether aromatase inhibitors can also be effective as preventive agents. An increasing literature also supports the beneficial role of the contraceptive pill in *BRCA* mutation carriers. Bonanni refers to a recent meta-analysis carried out by members of his department (*EJC* 46:2275–2284). "It shows the use of endocrine contraceptives in *BRCA* mutation carriers does not raise significantly the risk of breast cancer even if taken for a long time, but on the other hand it does decrease the risk of ovarian cancer by 50%."

"Of course SERMs don't cover the gap of ER-negative carcinogenesis," adds Bonanni. This is why research into other types of compound is so important." Such research includes everything from nonsteroidal anti-inflammatory drugs (NSAIDs) to statins and vitamins, especially vitamin D and retinoids, which are vitamin A derivatives. Much of this work has been funded so far by the US NCI, and led by pioneers like Michael Sporn, who first coined the term 'chemoprevention' (see *Cancer World* May–June 2006). But Europe has also made a contribution, not least Bonanni's team at the EIO, which has spent 20 years working on various potential chemopreventive agents, including fenretinide, a synthetic derivative of vitamin A. "A number of publications have found evidence of strong capability of this compound to reduce risk of breast cancer, and a good trend to reduce risk of ovarian too," says Bonanni. That evidence will be a lot clearer once the results of an ongoing phase III, double-blind placebo-controlled trial in women at high risk are known.

Bonanni is also enthusiastic about research into 'natural compounds' with cancer prevention properties, such as carcumin and green tea, and he believes advice on diet and exercise should be an integral part of cancer prevention.

As for the more radical options of risk-reducing surgery, Bonanni describes himself as 'a moderate', contrasting the approach of his department with what he calls 'extremists', who are quick to advise early prophylactic surgery "not only to gene mutation carriers." Though removing close to 100% of breast tissue has been shown to reduce risk even below the standard risk for non-mutation carriers, this can be hard to achieve even for experts, and the ideal of a zero risk level is unattainable, he argues.



There is more of a case to be made, he believes, for removal of the ovaries. "If you are still a fertile woman and have a risk of an ER+ cancer, as for example *BRCA*2 mutation carriers, removing the ovaries very early reduces your risk of breast cancer by around 50%. The primary drawback, of course, is that the woman loses her chance of having children through natural conception, which is one reason why Bonanni advocates a sequential approach to risk management, saving more radical options for later. "If you are at high risk, you can start sometimes very early in your lifetime with surveillance, which maybe should be increased over time. At a certain point, when the estimate of your risk increases, you may opt for a chemoprevention programme like entering a trial, and when these estimates increase further, you may need to go for a surgical prophylactic option."

For individual women and their medical advisers, adopting such a sequential approach in principle is only the first step. Getting the timing right can be tricky, and this is where knowledge of risks, risk reduction and counselling skills are so essential, and why Bonanni is advocating for specialist teams.

A service for the BRCA era

Europe now faces the challenge of organising services that translate our new-found insight about genetic cancer risk and risk management strategies into effective prevention. The UK has been ahead of the game, setting up regional genetics services in the 1990s, many of which developed distinct cancer genetics services. Rachel Iredale, who works as a research fellow with the Cancer Genetics Service for Wales, stresses the unique nature of the genetics services model in healthcare.

The unit of care is the family rather than the individual, and the service does provide the sort of support Francisca lacked in discussing how to raise the issue of a genetic predisposition to cancer with other family members. They can even help, "for instance by writing to the GPs of family members to say that somebody in the family has a bowel cancer and it might be worth screening people."

Bonanni advocates a sequential approach to risk management, saving more radical options for later

In the US people are encouraged to find out about their family history of cancer and take appropriate action

Another key aspect addresses Francisca's concern over long-term follow-up. "Once you are referred into the service you are with us for life," says Iredale. "We get a lot of 18-year-old women who have seen their mothers die of cancer, or their sisters or their aunts have got it, and they want to do something quite quickly. They can come for counselling, and they can re-access the service at any stage. As they get to particular milestones in their lives, when they want to get married or are thinking of having children, fears about cancer often re-emerge, so they can re-contact the service at any time."

Iredale has also been working with high-risk families to produce a series of around 50 digital stories (www.cancergeneticsstorybank.co.uk) to help people in similar situations, answering questions like: "What is it like to have a genetic counselling appointment?" "What feelings will I have if I go for genetic testing?" "How will I tell my kids that cancer is running in our family?"

Raising awareness among GPs, oncologists and other health professionals about the need to look for a family history of cancer is also part of the genetics services remit. "We have two questions that we give that are very sensible and a six-year-old could understand:

- Are there two or more close relatives with cancer on the same side of the family?
- Has any relative been under 45 when diagnosed with cancer?

What the service doesn't do, for the moment, is the sort of 'directive' public health work that is becoming common in the US, which encourages people to take responsibility for their own health by finding out about their family history of cancer and taking appropriate action. One suggestion from the US Surgeon General has been for people to discuss these issues when they gather at family occasions such as Thanksgiving – the so-called 'turkey talk'. The advocacy group FORCE – Facing Our Risk of Cancer Empowered – also aims to help people find out about their risk level and use that information to help them stay healthy.

The turkey talk. Finding out about the conditions and diseases that run in your family is a step everyone can take towards managing risks to their own health

Iredale is convinced that this is the way Europe needs to start thinking in the BRCA era. "Because we know more and more about the genetic components of common conditions, like heart disease, diabetes, asthma, there is a shift within certainly the academic and clinical communities to try to get people to use this information for health promotion and promoting good public health. We call it acquiring a genetic literacy."

She would like to see this public education start at primary school age, and has written a research proposal that could be the first step in moving towards the more proactive US 'empowerment' model. "Children need to know what role genetics plays in their family. And they need to learn that genetics isn't a scary word, cancer isn't a scary word, and they can have a lot of it in their families. They need to use that information in a way that helps them and encourages them to make good diet, lifestyle and reproductive decisions."

Desperately seeking a bone marrow match

The media campaign that made things happen in Romania

Peter McIntyre

CRISTINA NICHITUS

A powerful media campaign that is set to transform the prospects of Romanian patients in need of transplant treatments won TV journalist **Paula Herlo** an ESO Best Cancer Reporter award. The €5000 prize is the first in a new Campaigner category. She talked to *Cancer World* about how her Pro TV broadcasts mobilised public opinion behind the call for a national stem cell donor registry.

When TV journalist Paula Herlo travelled abroad to research a story on advanced treatments for patients with blood diseases, she discovered something about her own country that shocked her.

While looking at transplantation treatments for leukaemia at La Fundació Josep Carreras in Spain, Herlo was shown the European network for registries of bone marrow and T-cell transplant donors. One researcher offered to help her localise her story for her Romania Pro TV viewers. "She asked me 'Do you want to know how many donors Romania has on the registry?' When I said yes, she tried to find it on her computer. Then she told

Result. Former Health Minister Ioan Bazac (*opposite*) and Paula Herlo (*right*) were the first to be tested to be registered donors, under an approving media spotlight at the Ministry of Health, September 2009

me 'I can't do it; you don't have a registry.'"

Without an approved registry, neither the Romanian health system nor the patients waiting for treatment could link to the European Marrow Donor Information System (EMDIS), an international computer network of registries that covers more than 85% of stem cells donors worldwide. And without being part of the global network, the only chance that Romanian patients had of finding a bone marrow match was from close relatives.

When Herlo returned home she found that about 150 leukaemia patients a year were waiting in Romania for transplants, without much hope. There were also 3500 people with Hodgkin's disease and 3700 Romanian children with thalassemia major, many of whom could be treated with T-cells from bone marrow. Meanwhile, the three centres in Romania that carry out bone marrow transplants could only do so if they found donors within the patient's family.

"I realised at that moment that I must do a campaign, because in our country, if a patient has leukaemia and does not have a donor in his family, they are condemned, unless they have the money for treatment in France or elsewhere." To get treatment abroad costs anything from €75,000 to €150,000 – out of the question for most families, given that the wage for a teacher is about €350 a month.

Herlo's team at Pro TV agreed to launch a campaign, and haematologists in the country enthusiastically agreed to support them. In March 2009 Herlo began a series of interviews with families and patients that grabbed the attention of the public.

She highlighted cases like that of 18-year-old Dragos Croitoru, who waited three months while the health bureaucracy in Romania considered whether to send him abroad for treatment. Approval arrived on the day that doctors told his mother that he had only a week to live. "I don't even know if I have the strength to get out of bed anymore," he told Pro TV. "I feel that it's all over. I don't even have the strength to pick up a glass of water and drink."

Herlo's reports detailed unbearable foot dragging – including the five days it took the Bucharest Public Health Directorate to find a driver to deliver Dragos' papers to the Ministry for approval. She told her audience: "Dragos' story is illustrative of a flawed system that puts people's fate in the hands of bureaucrats for whom the lives of these patients don't mean anything. They are just files."

Dragos got to Israel for treatment where sadly he died. For him, the treatment had come too late.

A SUSTAINED CAMPAIGN

Over the next two months, Herlo and Pro TV ran 25 stories highlighting the need for a national registry under a slogan "Avem viata in sange" – "there is life in our blood". "We showed how patients are dying – abroad the survival rate is 80%, and in Romania it is 20%."

Out of the many tragic stories, it was the first that caused Herlo most heartache. Caludiu Voicu, an eight-year-old boy from Slatina, had waited a year for approval to be sent abroad for treatment, at a cost

"Dragos' story is illustrative of a flawed system that puts people's fate in the hands of bureaucrats"

The campaign was taken up by newspapers and blogs, and 36,000 people said they were prepared to be donors

of about €100,000. As a result of the campaign, he made it to Hungary, but his leukaemia was too far advanced. "He passed away last year – it was very hard. I helped his family get him treatment, but it was too late for him."

The campaign was taken up by newspapers and blogs, and 36,000 people signed up on the Pro TV website saying that they were prepared to become donors. After two months, the then Health Minister Ioan Bazac announced that Romania would set up a registry that would meet international criteria. In September 2009, live on TV, Herlo and the Minister became the first two people to be entered on registry as potential donors.

"It was a big surprise when they responded. It was like a dream. But when I had spoken to the Minister I told him that we would continue this campaign for a year or two years if necessary."

One of those who had been watching the campaign was Olga Cridland, president of the PAVEL Association Against Childhood Cancer in Romania. She says that scarcely a week goes by when she does not hear of a new patient who needs to be sent abroad for treatment. The campaign got patients and families talking and they became active supporters. Hugely impressed, Olga nominated Herlo for the Best Cancer Reporter Award.

"I think that the media has a big power in influencing things, depending on who is doing the campaign. If it is made in a really good and, how can I say, stubborn way, I think this can change many things regarding health, and changes in the laws. Our attitude as organisations is to try to work together with the media. When we heard Herlo's campaign I thought it was a very good way to do it."

Ethical pitfalls

Herlo recognises the potential ethical pitfalls in running a campaign based on highlighting tragedy and hope in people's lives, and stresses the importance of having a good team to take decisions. "My colleagues are very receptive to my ideas and support me very much – my boss is a great woman. Of course, there were discussions about ethics and I treated every case very carefully. But I admit that along the campaign there were very emotional moments, when families who lost their loved ones spoke about their drama and the chance that every Romanian patient should have."

Herlo says she would prefer to avoid these sorts of highly emotive, dramatic stories, "but experience showed me that the Romanian authorities react only to pressure from public opinion and the mass media. Sometimes we have to call things by their names and show that people suffer, so that the ones who can change their destinies react."

Media campaigns, she adds, can get things done, because the public becomes a partner. "They can ask the authorities to change things. I strongly believe that a media campaign can change laws and even mentalities."

Herlo, who has won awards for her reports on economic and social issues before she turned to health, is now running a series on the crisis in the Romanian health system, campaigning for a change in laws and funding. "Romania has an underfinanced health system. The funds are going into black holes, without anyone paying for it. The hospitals are going bankrupt one by one, and the patients are paying for treatment although they already pay the health insurance."

The implications for anyone diagnosed with cancer can be dire. "Cancer patients are somehow condemned in Romania. For example, once a patient is diagnosed he must wait for months sometimes for the treatment to be approved by Health Insurance Office."

Olga Cridland says that organisations like hers are learning to work more effectively with the media, inviting reporters to come and speak to patients directly. PAVEL has formed a partnership with the health channel Sanatatea TV and is also working with *Adevarul* newspaper ("The Truth") to highlight the need for early referral of children with

"Sometimes we have to show that people suffer, so that the ones who can change their destinies react"

DALILA DULGHERIU

Inspiration. Paula Herlo with Ramona Ilian, a little leukaemia patient she met on her visit to Barcelona's Vall D'Hebron hospital while researching her story on blood transplantation treatments

cancer, backed by the UICC 'My Child Matters' campaign.

PAVEL also appreciates the part of Herlo's latest health campaign that is pressing for government action to ensure that common cancer drugs are available on the Romanian market. Because the number of patients is relatively small, lower-cost drugs such as Cosmegen (dactinomycin) used in the treatment of Hodgkin's lymphoma, cannot be bought in Romania. "Unfortunately, we have a big economic crisis now affecting the entire health system," says Cridland. "Many people are suffering and we have tried to alert the authorities but it has not changed the situation. It is a tragedy because people have to travel abroad to buy this or that drug."

These are issues, she says, where a campaigning media can wake people up. "Not all media are good," she says. "I want to make a distinction. But if you speak to a proper journalist, sometimes they help you to express clearly what you want to say. I don't know about other countries, but I have a good impression about media in our country. When reporting on children, mostly the journalists are very sensitive."

While she campaigns on these broader health issues, Herlo has not given up the bone marrow registry. Of the 36,000 people who volunteered to sign up, so far only about half have actually done so. The registry is due to be linked to other international registers in February 2011, when it will finally become a resource for hope and treatment – and Herlo is not ready to let the matter drop. "This campaign will continue next year with a series about the importance of becoming a donor. I will prepare another campaign to sustain this register."

Given her record so far, Romanian patients in need of a transplantation treatment will soon be facing a much brighter future.

"Patients are paying for treatment although they already pay the health insurance"

Real compassion is about moving things forward

➜ Simon Crompton

The decision to focus on infections associated with cancer treatments, back in the early '70s, put **Jean Klastersky** on a path that would lead to him pioneering the field of supportive care in cancer. His research has helped establish the value of good communication, yet he warns that compassion in a doctor means more than empathy, and getting too emotionally involved can lead to burnout.

Professor Jean Klastersky is quite clear about his achievements, and what drove him towards them. It wasn't a personal commitment to help people with cancer. It was an early aspiration to contribute to scientific progress – to be a Great Physician: a Freud, a Babinski, an Osler.

It's not that compassion hasn't been intrinsic to his ground-breaking work on infection and cancer, and the development of supportive care. "But I always told myself that real compassion in a physician," he sums up succinctly, "is to keep things moving, to make progress."

And that's what he's done over 40 years. From carrying out early and influential trials on sepsis in neutropenia, through putting both supportive care and infection in cancer patients on the international map, to writing highly influential works on lung cancer and doctor burnout, Klastersky has pushed the cancer agenda forward.

In the early 1970s, when he was setting out on his work investigating infections related to cancer treatments, patients with acute leukaemia were (in his own words) still "dying like flies" before they reached remission. "I think that our concepts and research changed that a lot. Actually the improved care for patients with infection was the first example of supportive care in cancer medicine," he says.

Trim and still energetic in his 71st year, I'm speaking to him at the Institut Jules Bordet, a specialist cancer hospital and research unit in Brussels, where he was head of the Department of Medicine for 27 years until his official retirement in 2005. The institute is part of the Free University of Brussels, where he started his career and where he has remained for nearly its entirety.

Without a trace of vanity, he says that he would probably have succeeded in any area of medicine, acknowledging that ambition and occasional opportunism have moulded his career. He comes from an old Czech family "of low-rate nobility", which can be traced back to the 16th century. His family left Prague when he was six, at the end of World War II, when his father came to work at the Czech embassy in Brussels. But when the Communist Party took over in 1948, his family stayed in Brussels as political refugees, and

Klastersky has been based in Belgium ever since, raising his own family there.

It was the high-quality science teaching at a Belgian public school that gave him a commitment to go into medicine in his early teens. He was particularly inspired by a small book by the great French physiologist Claude Bernard, entitled *An Introduction to the Study of Experimental Medicine*. "Bernard defined the principle that the laboratory and the clinic should go together, and you should go from one to the other. I was very, very impressed by the concept." It was a crossover that ended up defining his career.

Training in internal medicine as an intern and then a resident at the Free University of Brussels between 1962 and 1965, he came under the influence of Henri Tagnon, who was trying to reshape the Institut Jules Bordet into one of the best cancer centres in the world. He suggested that the young Klastersky should start specialising in infectious diseases – particularly since the institute currently had to rely on external microbiology services. A Fullbright fellowship got him to Harvard Medical School where he spent three years as a chief resident and then research fellow.

One foot in the clinic one in the lab

He returned with a solid training in infectious disease, and in 1971 became the youngest associate of the Faculty of Medicine at the university. Tagnon gave him the responsibility of setting up a new microbiology lab on completely new principles. "I applied the principles that I discovered in the States – that the infectious disease concept has one foot in the clinic, and one foot in the lab. The whole service between the two was all directed by one person – that was me. It was a completely revolutionary concept."

Embodying the strong link between the lab and the patient, Klastersky had an opportunity to research and trial innovative treatments. He focused on research that would significantly improve survival rates in patients whose immune systems were compromised by chemotherapy, and developed the concept of synergistic antibiotics (effective combinations of different antibiotics) for neutropenic patients (who have low levels of neutrophil blood cells). He also developed the concept of endotracheal treatments for patients with gram-negative pneumonia (which are fed through the trachea).

As his work progressed, he looked on as Tagnon established, and then led (as president) the European Organisation for Research and Treatment of Cancer (EORTC).

A new type of treatment. Klastersky with palliative care specialists Gary Morrow (US) and Andreas Du Bois (Germany) discussing how to define 'supportive care' at one of the first meetings of the newly founded Multinational Association for Supportive Care in Cancer

"I saw this concept of European organisations and thought, why shouldn't we do that for infection in cancer patients?" So in 1973, with collaborators from the UK, US and Australia, he founded the EORTC international antimicrobial therapy cooperative group. Over 20 years it published 20 pivotal papers on infectious disease in immunocompromised patients. The first, in the *Journal of Infectious Disease* in 1976, reported on the first ever large randomised comparative study on the management of sepsis in neutropenic patients. It gave international relevance to the innovative activity in Brussels and it made Klastersky's name.

When Tagnon retired in 1977, Klastersky, at just 37, was chosen as his successor. But there was a problem: it would be unusual for the Head of Medicine at a world renowned oncology centre to be a specialist in infection rather than cancer. So straight after his appointment, Klastersky took a sabbatical of several months in America to train as an oncologist. It was a logical conclusion for him, further forging the links between oncology and microbiology.

At the institute, he made a point of seeing patients with all types of cancers and having as broad a perspective on medical oncology as possible. He became professor of medicine, professor of medical oncology, and professor of physical diagnosis, and the teaching his department provided attracted fellows from all over Europe. Under his stewardship, medical oncology beds expanded from 40 to 100, new haematology, intensive care, supportive care and psycho-oncology units were established, the research facility was expanded, the number of physicians increased from 15 to 60 and the research budget went up to €3 million.

The concept of supportive care

It was his broad insight into the factors that affect the welfare of patients with cancer apart from the cancer itself that gave rise to the concept of supportive care, for which Klastersky is arguably most famous. Thousands of oncologists around the world have read his handbook *Supportive Care in Cancer.*

He focused on improving survival in patients whose immune systems were compromised by chemotherapy

Klastersky is keenly aware that definitions of supportive care differ from country to country and are hotly debated by health professionals. But in 1992, when he and Hans-Jörg Senn of the St Gallen Tumour Detection and Prevention Centre in Switzerland created the Multinational Association for Supportive Care in Cancer (MASCC), things were clear.

"Something was definitely going on at that time," he says. "We felt that supportive care was really a fifth modality in cancer treatment and should be to some extent separate from other modalities." The definition they came up with was simple. "It was all the care you provide to cancer patients outside specific anticancer therapy. It means you are preventing complications not only related to the cancerous disease itself, but also related to the therapy. Supportive care starts with the diagnosis of cancer, and goes through the whole evolution, encompassing psychological support, end of life, pain, antiemetics, antibiotics and so on. Besides anti-cancer therapy, everything is supportive care."

The concept worked well, says Klastersky. There was a need for specific research in the area, dedicated meetings, and medical oncologists with a particular interest. It is a mark of how well the important principles of supportive care are now understood that they have become integrated into cancer care, and are no longer seen separately, he believes.

"I think medical oncologists now understand that it is a question of quality of life, as well as quantity of life. The patient also understands this, and requires this perspective. Attention to quality of life necessitates all the supportive care methods being integrated into medical oncology, and this happens at the good centres. They need to be seen to have a supportive care programme."

Good communication between clinician and patient is an intrinsic part of good supportive care, and this is another area where Klastersky made his mark. The institute's onco-psychiatry unit trains Belgian physicians in good communication techniques, and its supportive care unit provides intensive support – and plenty of talking time – for patients with chronic problems related to their illness, such as pain. His research has indicated the value of good communication to patients and clinicians alike.

Here again things are improving on an international level. Laws and regulations in some European countries now compel clinicians to tell patients the truth, and make clear what they know and what they don't know. And multidisciplinary working has made treatment decisions better discussed and more democratic.

"I think that doctors coming along and telling people what to do has almost completely disappeared," he says. "I think that patients are also becoming more aware that things aren't always black and white, and that decisions might be complicated and need discussing."

It's an optimistic viewpoint. In fact Klastersky is generally extremely positive about the way cancer services are progressing internationally. "I often think of the picture on the front of *Scientific American* in 1971, with President Nixon signing the National Cancer Act, and declaring war on cancer. Well, of course, cancer is still here, but since then so much energy has been devoted to fighting it that 40 years later we can see a tremendous difference – particularly technological achievements that are making cancer a type of chronic disease."

Who sees the patient as a whole?

But he does have worries. If his own career has been testimony to the benefits of acquiring as wide a perspective on cancer as possible, it is not surprising that his main concern about the future of medicine is how limited the field of vision of many physicians is becoming.

"My fear is that the training of the oncologist will become more and more narrow. I can see that you can

Focus on febrile neutropenia. With Canadian specialists Ron Feld of the Princess Margaret Cancer Center, in Toronto (*right*), and Andy Padmos, then head of medical oncology at King Faisal's Hospital, Saudi Arabia, at an early international meeting on preventing and treating one of the most serious side-effects associated with some chemotherapy regimens

A transatlantic supportive alliance. Stephen Schimpff, head of the University of Maryland Cancer Center in Baltimore, Maryland (*left*), organised the first symposium on supportive care in 1987, and is pictured here in Brussels for the second symposium held a year later. Also pictured is Klastersky's wife Marie-Thérèse Klastersky-Genot, an oral surgeon specialised in treating patients with severe oral mucositis

have breast cancer people who do not go into the treatment of colorectal cancer, and that you might have people within breast cancer who are more specialised in hormonal therapy, for example. But it worries me that, at some point, too many medical oncologists will have very sophisticated medical skills but will fail to really see the patient as a whole. I think we should be very attentive that medical oncology remains a broader type of activity." He remembers witnessing at one hospital six different specialists attending a patient – none of them was taking overall responsibility for the patient. If something went wrong, would they all blame someone else, he wondered.

"I come from general internal medicine, and I know it's tough nowadays not all to specialise in small areas. But I think there's a potential danger when you don't have one person who can clearly put together the whole picture of a patient under one head."

Fascinatingly, another worry surrounds doctor–patient communication: not lack of it, but too much. For all his research showing the benefits of good communication, Klastersky has also demonstrated that it can be counterproductive if physicians become too emotionally involved with patients. In a paper on physician burnout published in the *Journal of Cancer Education* last year (March 2010) his team of researchers found that heavy clinical workload and the overuse of facilitative communication skills were associated with cancer physician burnout.

"I think that sometimes, if communication becomes too detailed, a mutual emotional involvement begins which can be very difficult for some physicians – it's closely related to their personalities. We had a very nice medical oncologist here, who burnt out completely. Her problem was that she spent hours discussing issues with one patient, and she was no longer the solution, she was part of the problem."

"It's very difficult to regulate, and every personality is different, but you need to maintain emotional detachment." That's why he believes the physician's role transcends relationships. It's about making progress.

If there's one small hint of regret from Klastersky during our conversations, it centres on his specialism in lung cancer. Not long after he became Head of the Department of Medicine at the Institut in 1977, he decided to make lung cancer a specialty – mainly, he acknowledges, because "[I] had to make myself known" in the field of oncology, and most areas apart from lung cancer already seemed to be well-served with experts at the institute.

He created the EORTC Lung Cancer Working Party, and was president between 1978 and 2003. The group's first study demonstrated that cisplatin was active in non-small-cell lung cancer. Its second demonstrated that the combination of cisplatin plus VP16 was active. A series of influential studies followed over the next 10 years.

Yet concentrating increasingly on supportive care in the 1990s distracted him from achieving more in this area, he believes. "I think it was a mistake for me when I decided not to be more super-active in the field of lung cancer," he says. "I could have been more successful in that field."

"Every personality is different, but you need to maintain emotional detachment... It's about making progress"

"For all your passion and values, if you don't know your weaknesses, you may not succeed"

A WINNING FORMULA

Klastersky is conscious of his deep desire to achieve. He analysed it and broke it down last year when asked by the MD Anderson Cancer Center in Houston to talk to fellows about the recipe for a successful medical career. "First, you need the person to be driven by an internal passion – the need to be a physician or whatever. Then you need values, so you know what to do with your passion – to make money, or leave a message for posterity and so on. Then you need to be able to evaluate your skills, to be aware of your strengths and weaknesses. And for all your passion and values, if you don't know your weaknesses – for example being too empathetic with a patient – you may not succeed. You may burn out."

A "relatively peaceful life", he adds, is an important factor for success in any professional career, "and I was lucky enough to have an understanding and supportive wife to share the good and less good aspects of it."

The acclaim he's received throughout his career – he's won the Guy R Odom Award in 1990 for outstanding achievements in infectious disease research, the Lucien Cox Award in 1997, the Louise Biernaux Foundation Award in 2001 and the Hoyez-Van Cutsem Award in 2003 – testifies that the formula has worked pretty well for him.

Still seeing patients as a consultant at the Institut Jules Bordet, he's now co-ordinating a programme of collaboration between nine Brussels cancer hospitals called the 'programme des soins oncologiques'. Looking back, he says, it's the teaching aspect of his role – the passing on of knowledge and experience to others, that he has found perhaps most satisfying. As professor of medicine at the faculty of medicine, Free University of Brussels, he spent 30 years teaching until 2005. He is still attending professor at Charles University in Prague, where he goes every three months to give a series of lectures (in Czech).

Aside from the enjoyment it gives him, teaching gives Klastersky a sense that he's filled in the picture of a great physician that he started drawing in his schooldays.

Passing on the baton. In 2005 Klastersky ceded leadership of the Jules Bordet Department of Medicine to Martine Piccart, after 27 years in the post

"I always thought that this idea of the great physician carried with it the need to transmit important messages – by communication, but also by example. That's been important to me, and has taken a substantial amount of my time."

"Again, you have to know what your values are. It has often been said to me that I didn't achieve all I could have on the political side – making a career in EORTC, for example, and becoming President. But you cannot do everything at the same time, and you have to make your choices according to your values. My values are more to do good international research, good teaching."

And are there any particular ways in which he would like his students to follow his example? "As long as oncologists make efforts to keep themselves competent and continue to see the patient rather than the tumour, there is no better recipe than that."

Gemcitabine alone or plus cisplatin for biliary tract cancer?

Werner Scheithauer

A randomised phase III trial comparing cisplatin plus gemcitabine with gemcitabine alone for patients with advanced biliary tract cancer has provided evidence for a new standard treatment option for these patients. The therapeutic outcome (overall survival, disease-free survival and disease control rate) was significantly better in the combination arm, with no increase in toxic effects.

Advanced biliary tract carcinoma (ABTC) is a heterogeneous malignant disorder of the digestive tract that has a poor prognosis and is rare in the Western world. Very few treatment options are available for ABTC, owing to a paucity of definitive studies assessing chemotherapy regimens. The rationale for the use of chemotherapy was justified by a study published in 1996 by Glimelius et al.[1], which suggested a survival and a quality of life advantage for patients treated with chemotherapy compared with those who received best supportive care alone.

Numerous small nonrandomised studies of various anticancer chemotherapeutic drugs and combinations of such drugs for ABTC have been published. A pooled analysis of 104 palliative chemotherapy trials in ABTC (a total of 112 trial arms and 2810 patients) reported a tumour response rate of 22.6%, a disease control rate of 57.3%, a median time to progression of 4.1 months, and a pooled overall survival of 8.1 months.[2] Single-agent antimetabolites (5-fluorouracil or gemcitabine) seemed to be more active than other single agents (such as anthracyclines, taxanes and topoisomerase I inhibitors). Furthermore, combined treatments of antimetabolites with platinum salts (cisplatin, oxaliplatin or paraplatin) were superior to other agents and drug combinations.[2] On the basis of these findings, UK investigators initiated a randomised phase II study to compare cisplatin plus gemcitabine with gemcitabine alone, which was subsequently extended to a phase III trial.[3] The study by Valle and colleagues is a pragmatic, well-conducted trial, appreciating the need for multidisciplinary patient management. This trial incorporated biliary stenting in 45% of all patients in both treatment arms. Maintenance of biliary drainage is critical in patients with advanced biliary tract cancer. Aside from the essential quality of life benefit, biliary drainage is a prerequisite for chemotherapeutic drug administration

nature REVIEWS CLINICAL ONCOLOGY

This article was first published in ***Nature Reviews Clinical Oncology*** 2010 vol.7 no.10, and is published with permission. doi:10.1038/nrclinonc.2010.130, www.nature.com/nrclinonc

and counteracts potentially life-threatening biliary sepsis.

Valle and co-workers recruited a total of 410 patients with locally advanced or metastatic cholangiocarcinoma, gallbladder or ampullary cancer. These patients were randomly assigned to an outpatient chemotherapy regimen with either cisplatin (25 mg/m^2) plus gemcitabine (1000 mg/m^2) on days 1 and 8 every three weeks, or gemcitabine alone (1000 mg/m^2) on days 1, 8, and 15 every four weeks for up to 24 weeks in both arms.[3] The primary endpoint – a significant improvement in median overall survival with combination chemotherapy compared with gemcitabine alone – was clearly met (11.7 months vs 8.1 months; HR 0.64; $P<0.001$). Similarly, significant increases in the median progression-free survival (8 months vs 5 months; $P<0.001$) and the rate of tumour control (complete or partial response or stable disease, 81.4% vs 71.8%; $P=0.049$) were observed in the experimental arm, importantly with no increase in toxic effects relative to gemcitabine alone. On the basis of these results, the authors conclude that cisplatin plus gemcitabine is an appropriate option for the treatment of patients with ABTC.[3]

These data are consistent with the known preclinical[4] and clinical synergies[5,6] of cisplatin and gemcitabine in other malignancies, such as lung cancer and head and neck cancer, and previous phase I and phase II trials in ABTC.[2] The findings are also supported by the results of a randomised trial involving 83 Japanese patients with ABTC, treated with the same regimens, which were presented at the 2009 ASCO Annual Meeting. That trial reported a median overall survival of 11.2 months in the cisplatin plus gemcitabine group compared with 7.7 months in the gemcitabine-only group.[7] The study by Valle et al.[3] provides an outstanding contribution to the field as it is the very first randomised trial sufficiently powered to define an active treatment regimen in ABTC. Owing to the smaller number of patients and heterogeneous patient population in ABTC as compared with other common malignancies, phase III trials have been a challenge to conduct. The authors have successfully overcome this inherent problem, assisted by an effective coordination of national clinical research efforts. This UK study has not only defined a new standard of care, but also demonstrated that it is feasible to perform large-scale studies in ABTC. Furthermore, despite inherent difficulties in assessing objective response in this disease entity, the authors have succeeded to do so using RECIST criteria. These objective response data were obtainable in at least 74% of their patients who presented with measurable disease (a non-prerequisite for study entry). The findings of this trial also go against previous beliefs that gallbladder cancer and cholangiocellular cancer subgroups vary in the rate of chemotherapeutic responsiveness. For example, Eckel et al.[2] reported a greater likelihood of objective response (36% vs 18%) but inferior overall survival time (7.2 months vs 9.3 months) in patients with advanced gallbladder cancer relative to those with cholangiocarcinoma. The Valle et al.[3] study is in contrast to the rather contradictory findings of this retrospective pooled analysis of previous palliative chemotherapy trials in ABTC.

The biology of biliary tract cancers seems to be in the spectrum of gastrointestinal epithelial cancers with similar oncogenic mutations.[8,9] Key oncogenic mutations in biliary tract cancers include *KRAS*, *EGFR*, and *BRAF*, potentially offering a genetic basis for tailored first-line regimens with targeted agents as has been demonstrated in colorectal cancer.[10] In view of the urgent need for further improvements in the effectiveness of anticancer treatment in ABTC, anti-angiogenic drugs, EGFR inhibitors, inhibitors of BRAF or the downstream MAPK/MEK pathway and other promising novel biologicals warrant investigation. Such testing should be done through well-conducted prospective clinical trials with companion biological exploration to better understand the optimal place of such drugs in ABTC. The study by Valle et al.[3] has been an important contribution for such future trials. The study has firmly established a new classic cytotoxic regimen as standard of care and demonstrated the need and feasibility of coordinated national and international clinical research efforts, which are of paramount importance to continued progress in this field and improved outcomes for our patients.

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

Practice points

- The combination of cisplatin plus gemcitabine is an effective palliative treatment option in patients with locally advanced or metastatic cholangiocarcinoma, gallbladder or ampullary cancer.
- The demonstration from a randomised phase III trial that cisplatin plus gemcitabine significantly improves disease control rate, progression-free survival and overall survival, with no increased toxic effects compared with gemcitabine alone, confirms this regimen as the new standard treatment for advanced biliary tract carcinoma.

Author affiliations: Department of Internal Medicine and Cancer Center, Medical University of Vienna, Vienna, Austria

Molecular selection for 'smart' study design in lung cancer

Amanda Psyrri and Barbara Burtness

The ZODIAC trial reported that the addition of vandetanib to docetaxel in second-line treatment of unselected patients with metastatic non-small-cell lung cancer resulted in a statistically significant improvement in progression-free survival compared with docetaxel alone. Identification of biomarkers to assist in molecular selection of patients for targeted therapy is a tool for 'smart' clinical trial design.

Patients with advanced or metastatic non-small-cell lung cancer (NSCLC) have a dismal outcome. Platinum-based chemotherapy is the standard first-line treatment; however, this approach yields disappointing median survival rates that do not exceed one year. Molecularly targeted agents that block pivotal pathways in cancer progression and can reverse chemoresistance seem promising. EGFR inhibitors and anti-angiogenic compounds have demonstrated marginal benefit in unselected cohorts of patients with advanced NSCLC. However, the superiority of gefitinib over chemotherapy was demonstrated in a molecularly selected population of patients bearing a sensitising *EGFR* mutation.[1] Novel molecular therapies such as those targeting the insulin-like growth factor 1 receptor or the EML4–ALK fusion protein have shown promising results in preliminary studies. Other targeted therapies acting on RAS/RAF/MEK, PI3K/AKT/mTOR or MET kinase are being studied in clinical trials, especially in resistant patients.

Patients with advanced NSCLC will eventually relapse or develop resistance to first-line treatment. Several chemotherapy agents, such as docetaxel and pemetrexed, have shown activity and have been approved by the FDA for second-line treatment of advanced or metastatic NSCLC. Docetaxel is associated with response rates between 15% and 20%, overall survival of 8.3 months and one-year survival rates of up to 37%.[2] A meta-analysis that evaluated the benefit of two-drug combinations versus single-agent chemotherapy in the second-line setting and demonstrated improvements in response rates with two-drug combinations did not translate into improvements in progression-free survival (PFS) or overall survival.[3] In addition, the two-drug combinations were associated with substantial toxic effects.

A rational approach to improve activity in the second-line setting might be the combination of a targeted agent with conventional single-agent chemotherapy. Several targeted therapies have been tested in the second-line setting. Erlotinib is an EGFR tyrosine kinase inhibitor (TKI) approved for second-line therapy in NSCLC. A randomised study comparing erlotinib with placebo showed improvement in median overall survival (6.7 months vs 4.7 months) and quality of life across all patient subgroups within the erlotinib arm.[4] Gefitinib, another EGFR TKI with a different pharmacokinetic profile to erlotinib, failed to yield a

nature REVIEWS CLINICAL ONCOLOGY

This article was first published in ***Nature Reviews Clinical Oncology*** 2010 vol.7 no.11, and is published with permission. © 2010 Nature Publishing Group. doi:10.1038/nrclinonc.2010.156, www.nature.com/nrclinonc

survival advantage in a phase III trial.[5]

A new study has reported promising results using vandetanib in combination with docetaxel to treat patients with advanced NSCLC.[6] Vandetanib is an oral inhibitor of EGFR and VEGF signalling pathways. The agent also targets the rearranged during transfection (RET) tyrosine kinase, an important growth factor in thyroid and other cancers. Vandetanib reverses primary or acquired resistance to EGFR TKIs in xenograft models of human NSCLC, particularly in resistant tumours with high tumour-derived and host-derived VEGF levels.[7] In a randomised phase III trial of second-line therapy for NSCLC, vandetanib single-agent therapy demonstrated equivalent efficacy to erlotinib, but with additional toxic effects (such as diarrhoea, hypertension and asymptomatic QTc prolongation).[8] Vandetanib improved PFS in combination with docetaxel, compared with docetaxel alone, in a randomised phase II trial.[9] An interesting subset analysis suggested the benefit was greatest for women.[9]

Herbst et al.[6] have now reported results from a randomised, double-blind, phase III study (the ZODIAC trial) to confirm the PFS benefit of adding vandetanib (100 mg) to docetaxel in advanced NSCLC. The study included 1391 patients randomly assigned to receive vandetanib 100 mg daily plus docetaxel or placebo plus docetaxel. Docetaxel could be given for up to six 75 mg/m^2 doses (or 60 mg/m^2 for patients treated in Japan) on a three-week schedule. The primary objective was a 20% improvement in PFS. The outcomes in women were also analysed independently to the whole study population.

The ZODIAC study demonstrated a very modest but significant gain in median PFS of 0.6 months (4 months with vandetanib vs 3.2 months with placebo, $P<0.0001$) and a similar PFS gain in women (from 4.2 months to 4.6 months in the placebo and vandetanib groups, respectively). Herbst and colleagues observed no improvement in overall survival, and only a 6% difference in the proportion of patients who had disease progression by six months after treatment. This small improvement in PFS occurred at a cost of substantial toxic effects; grade 3 and 4 adverse events including rash, leukopenia, neutropenia, and neutropenic fever were more common in the vandetanib group than in the placebo group, and QTc prolongation requiring dose interruption was noted in nearly 2% of patients. A longer time to deterioration of lung cancer symptoms was also reported in patients receiving vandetanib. Interestingly, the median exposure to docetaxel was only four cycles (or approximately 12 weeks) in each arm, and importantly, monotherapy with vandetanib continued in the experimental arm, while no active therapy was used in the placebo arm after discontinuation of docetaxel. A weakness of the study, as the authors point out, is that despite PFS being the primary endpoint there was no independent blinded review of radiological evaluations.

A phase III comparison of pemetrexed plus vandetanib versus pemetrexed alone in previously treated patients with NSCLC (the ZEAL trial) did not meet the primary endpoint of statistically significant PFS prolongation.[10] Similar to the ZODIAC trial, the ZEAL study demonstrated a significantly higher overall response rate and symptom control in the vandetanib group compared with pemetrexed alone.

The increase in PFS of borderline clinical significance with an increase in toxic effects and no improvement in overall survival, reported in the ZODIAC trial, taken in the context of the negative ZEAL trial, are unlikely to impact the current standard of care in patients receiving second-line treatment. For good responders to first-line chemotherapy, single-agent chemotherapy such as docetaxel or pemetrexed constitutes a rational choice with fewer toxic effects. EGFR TKI is preferred in patients with poor response or tolerance to first-line chemotherapy.

The results reported by Herbst et al.[6] underscore the vital importance of incorporation of molecular selection into the future design of clinical trials that use targeted therapies. For example, *EGFR* mutations are considered predictive biomarkers of high clinical benefit with EGFR TKI therapy, especially for first-line treatment. Herbst and co-workers did not present a subgroup analysis of tumour and circulating biomarker data including *EGFR* mutation status, as the analysis is still ongoing. Inhibition of VEGF and RET signaling may have also contributed to the antitumour efficacy of vandetanib.

A personalised approach to treatment selection is the future of lung cancer management in all lines of therapy. Such an approach may require tumour re-biopsy before administration of second-line therapy to identify, for example, known biomarkers of resistance to EGFR TKI. Noninvasive approaches, such as biomarker analysis on circulating tumour cells and blood biomarkers predictive of response or resistance, hold promise for treatment selection. Unfortunately, for most targeted therapies, clinically validated biomarkers have not been identified, and this remains a critical focus of research in the field.

Practice points

- The combination of a chemotherapy drug and a molecular-targeted agent appears to be a rational approach for previously treated patients with advanced NSCLC; however, clinical trials in un-selected patient cohorts often fail to demonstrate substantial survival benefit.
- Identification and validation of biomarkers for response or resistance will assist in the development of personalised targeted strategies in advanced NSCLC.

References

1. TS Mok et al. (2009) Gefitinib or carboplatin–paclitaxel in pulmonary adenocarcinoma. *NEJM* 361:947–957
2. N Hanna et al. (2004) Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *JCO* 22:1589–1597
3. M Di Maio et al. (2010) Clinical assessment of patients with advanced non-small-cell lung cancer eligible for second-line chemotherapy: a prognostic score from individual data of nine randomised trials. *Eur J Cancer* 46:735–743
4. FA Shepherd et al. (2005) Erlotinib in previously treated non-small-cell lung cancer. *NEJM* 353:123–132
5. N Thatcher et al. (2005) Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 366:1527–1537
6. RS Herbst et al. (2010) Vandetanib plus docetaxel versus docetaxel as second-line treatment for patients with advanced non-small-cell lung cancer (ZODIAC): a double-blind, randomised, phase 3 trial. *Lancet Oncol* 11:619–626
7. GN Naumov et al. (2009) Combined vascular endothelial growth factor receptor and epidermal growth factor receptor (EGFR) blockade inhibits tumor growth in xenograft models of EGFR inhibitor resistance. *Clin Cancer Res* 15:3484–3494
8. RB Natale et al. (2009) Vandetanib versus erlotinib in patients with advanced non-small cell lung cancer (NSCLC) after failure of at least one prior cytotoxic chemotherapy: a randomized double-blind phase III trial (ZEST) [abstract]. *JCO* 27 [Suppl. 15]:8009
9. JV Heymach et al. (2007) Randomized, placebo-controlled phase II study of vandetanib plus docetaxel in previously treated non small-cell lung cancer. *JCO* 25:4270–4277
10. R De Boer et al. (2009) Vandetanib plus pemetrexed versus pemetrexed as second-line therapy in patients with advanced non-small cell lung cancer (NSCLC): a randomized, double-blind phase III trial (ZEAL) [abstract]. *JCO* 27 [Suppl. 15]:8010

Author affiliations: Second Department of Internal Medicine, Propedeutic, University of Athens Medical School, Attikon University Hospital, Athens, Greece (Amanda Psyrri); Department of Medical Oncology, Division of Medical Sciences, Fox Chase Cancer Center, Philadelphia, USA (Barbara Burtness)

NEWSROUND

Selected reports edited by Janet Fricker

Functional limitations following breast cancer treatment influence mortality

→ JNCI

Physical limitations following breast cancer treatment, defined as reported difficulties in the completion of tasks of everyday living, can have far-reaching effects on how long women live, a US study has found. Older breast cancer patients in particular, and those who are overweight, are more likely to experience functional impairments for at least 18 months after treatment. The research indicates that the health of breast cancer survivors could be greatly improved with simple modifications in habits, such as becoming more physically active.

Breast cancer survivorship is increasing due to improvements in early detection and adjuvant therapy. Since overall survival is considered the most therapeutically relevant outcome for cancer patients, little attention has been paid to the physical limitations and other health problems affecting women who have had breast cancer. But the recent US Institute of Medicine report emphasised the need to identify high-risk breast cancer populations who could be targeted with interventions to promote quality and length of life.

To determine how physical limitations following initial breast cancer treatment affect morbidity and mortality among women who have had breast cancer, Dejana Braithwaite and colleagues from the University of California, San Francisco, studied 2202 women diagnosed with stage I, II or III breast cancer between 1997 and 2000. The women were followed for up to 11 years after diagnosis.

Baseline questionnaires, completed on average 21 months after diagnosis, asked participants about endurance, strength, muscular range of motion and small muscle dexterity following initial treatments such as chemotherapy, radiation therapy or hormone therapy. The study then explored the extent to which the impact of functional limitations on survival differed as a function of age, body mass index (BMI), tumour stage and other lifestyle characteristics.

Results show that at least one functional limitation was present in 39% of study participants. The authors found that functional limitations increased with age - 39.3% of women with one or more functional limitation were aged 65 to 79 versus 23.8% of those without any functional limitation ($P<0.001$). Women with limitations were also more likely to be overweight or obese – 35.7% of women with one or more functional limitations had a BMI of at least 30, versus 21.4% of women without limitations ($P<0.001$).

More women with functional limitations died from causes other than breast cancer – 8.9% of women with versus 2.7% without limitations ($P<0.001$). In contrast, similar proportions of patients with and without functional limitations died of breast cancer ($P=0.99$)

"A new finding from this analysis among longer-term breast cancer survivors is that functional limitations following initial adjuvant treatment primarily affect overall and competing-cause survival, but not breast cancer-specific survival," write the authors. The study, they add, underscores the need to track long-term effects and explore whether they are amenable to interventions. "...functional status may be an important addition to clinical screening among breast cancer patients to identify groups that are at high risk of poor prognosis, allowing the targeting of functionally impaired patients to improve quality and length of life."

Limitations of the study include the fact that information on physical impairments was available only after initial treatment so that functional limitations prior to cancer diagnosis could not be evaluated. The lack of a control group also meant that the effect of physical limitations on mortality could not be compared between women with and without breast cancer.

In an accompanying commentary, Harvey Jay Cohen from Duke University Medical Center (Durham, North Carolina), writes that the study's conclusions could be incorporated into a cancer survivorship plan, especially for elderly survivors. "Such an evaluation could guide therapy regarding underlying co-morbidities and other reasons for functional decline, such as obesity and decreased physical activity."

■ D Braithwaite, WA Satariano, B Sternfeld et al. Long-term prognostic role of functional limitations among women with breast cancer. *JNCI* 6 October 2010, 102:1468–1477

■ HJ Cohen. Functional assessment and the cancer survivor: something old, something new. *ibid*, pp 1450–1451

Reduced-intensity treatment delivers similar benefits to standard therapy in early Hodgkin's lymphoma

→ New England Journal of Medicine

Patients with early-stage Hodgkin's lymphoma showed similar rates of disease control regardless of whether they were treated with standard or reduced-intensity chemotherapy and radiation, a study from the German Hodgkin

Study Group (GHSG) has concluded.

The integration of the chemotherapy regimen consisting of doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) with radiation therapy resulted in greater efficacy and allowed the radiation field and dose to be reduced, leading to widespread use of the combined approach in patients with early-stage Hodgkin's lymphoma and a favourable prognosis. Four cycles of ABVD followed by 30 Gy of involved-field radiation therapy is now regarded as the standard of care by many groups.

In 1998 the GHSG initiated the HD10 study to investigate whether fewer cycles of chemotherapy and lower doses of radiotherapy could be delivered while maintaining high rates of disease control in patients with early-stage Hodgkin's lymphoma and a favourable prognosis.

Between May 1998 and January 2003, GHSG investigators, led by Andreas Engert, from the University Hospital of Cologne (Germany) randomly assigned 1370 patients with newly diagnosed Hodgkin's lymphoma and a favourable prognosis in a 1:1:1:1 ratio to one of four treatment groups – four cycles of ABVD followed by 30 Gy radiation (group 1, *n*=346), four cycles of ABVD followed by 20 Gy radiation (group 2, *n*=340), two cycles of ABVD followed by 30 Gy radiation (group 3, *n*=341), or two cycles of ABVD followed by 20 Gy of radiation therapy (group 4, *n*=343). Patients were recruited and treated at 329 hospitals and outpatient practices in Germany, Switzerland, the Netherlands, the Czech Republic and Austria. The primary outcome was freedom from treatment failure, with secondary endpoints including progression-free survival, complete response and treatment toxicity.

Results show that, at five years, rates of freedom from treatment failure were 93.0% for the four-cycle ABVD regimen versus 91.1% for the two-cycle regimen (*P*=0.39). Among patients randomised to four cycles of ABVD, five-year rates of freedom from treatment failure were 92.8% with 20 Gy compared with 93.1% with 30 Gy. Patients treated with two cycles of chemotherapy had 90.9% freedom from treatment failure with 30 Gy and 91.2% with 20 Gy. The intention to treat analysis showed no significant differences between the two chemotherapy groups for the secondary endpoints of overall survival (*P*=0.93) and progression-free survival (*P*=0.28).

Grade 3 to 4 adverse events occurred in 51.7% of patients treated with four cycles of ABVD versus 33.2% receiving two cycles (*P*<0.001). Additionally, grade 3 to 4 adverse events occurred in 8.7% of patients who received 30 Gy versus 2.9% who received 20 Gy (*P*<0.001).

"In summary, the HD10 trial showed that in patients with early-stage Hodgkin's lymphoma and a favourable prognosis, treatment with two cycles of ABVD followed by 20 Gy of involved-field radiation therapy is as effective as, and less toxic than, four cycles of ABVD followed by 30 Gy of involved-field radiation therapy," write the authors.

The overall survival rate of 94.8% at eight years for all patients in the study, add the authors, may suggest that some patients are still being overtreated. The introduction of positron-emission tomography, they add, might help identify patients who can be cured with even less treatment.

■ A Engert, A Putsches, HT Each et al. Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *NEJM* 12 August 2010, 363:640–652

Ovarian cancer strategies demonstrate similar survival

➜ New England Journal of Medicine

Neoadjuvant chemotherapy followed by interval debulking surgery was shown to be non-inferior to primary debulking surgery followed by chemotherapy in patients with bulky stage IIIC or IV ovarian cancer, a collaborative study by researchers from the EORTC Gynaecological Cancer Group and the Clinical Trials Group of the Canadian NCI has reported.

Primary debulking surgery followed by adjuvant chemotherapy is the standard of care for patients with advanced ovarian cancer. However, in several prospective studies investigators have evaluated outcomes with neoadjuvant chemotherapy before cytoreductive surgery as an alternative approach. One meta-analysis of such trials showed worse outcomes for those receiving neoadjuvant chemotherapy compared with those undergoing primary surgery.

Between September 1998 and December 2006, 632 patients from 59 centres in eight countries with stage IIIc or IV epithelial ovarian carcinoma, fallopian tube carcinoma or primary peritoneal carcinoma were randomised to primary debulking surgery followed by platinum-based chemotherapy (*n*=336) or to neoadjuvant platinum-based chemotherapy followed by debulking surgery (*n*=334). The primary endpoint was overall survival with the trial statistically powered to evaluate non-inferiority of the neoadjuvant chemotherapy versus primary surgery.

After a median follow-up of 4.7 years, results show that patients with neoadjuvant chemotherapy had a median overall survival of 30 months versus 29 months for patients receiving primary surgery. Subgroup analysis failed to identify any patient or tumour characteristics that were associated with better outcomes with one treatment than the other.

For both treatment groups the strongest predictor of overall survival was complete resection of all macroscopic disease. For the primary surgery group, median overall survival was 45 months for patients who had no residual tumours, 32 months for patients with residual tumours measuring 1–10 mm, and 26 months for patients with residual tumours greater than 10 mm. For the group receiving neoadjuvant therapy, the corresponding figures were 38, 27 and 25 months respectively.

"In conclusion, among patients with advanced (stage IIIC or IV) ovarian, fallopian-tube, or peritoneal ovarian carcinoma, survival after neo adjuvant chemotherapy followed by interval debulking surgery is similar to survival after primary debulking surgery followed by chemotherapy," write the authors, led by Ignace Vergote from Leuven University Hospitals (Belgium).

Given these findings and the results of other studies, the authors suggest that the goal of therapy should be the elimination of all macroscopic residual disease, rather than the elimination of lesions larger than 1 cm in diameter. "A potential drawback of neo adjuvant

chemotherapy followed by debulking surgery is that the occurrence of fibrosis after chemotherapy may make complete resection of macroscopic disease more difficult," write the authors.

The standard of care for women with stage IIIB or earlier-stage epithelial ovarian cancer (a group with a better prognosis) remains primary cytoreductive surgery, say the authors, adding that it is also important to rule out primary tumours of gastrointestinal origin when selecting patients for neoadjuvant chemotherapy.

■ I Vergote, CG Tropé, F Amant et al. Neo adjuvant chemotherapy or primary surgery in stage IIIC or IV ovarian cancer. *NEJM* 2 September 2010, 363:943–953

Less-invasive lymph node surgery is safe in breast cancer

➜ Lancet Oncology

Breast cancer patients with biopsies detecting no cancer cells in the sentinel lymph nodes who avoided axillary lymph node dissection (ALND) showed the same overall survival at eight years as women who underwent ALND, reports the largest ever randomised trial of breast cancer surgery.

Sentinel lymph node (SLN) surgery was designed to minimise the side-effects of lymph node surgery but still offer equivalent outcomes to ALND. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial, led by David Krag from the University of Vermont (Burlington, Vermont), set out to establish whether SLN resection achieves the same survival and regional control as ALND.

Between May 1999 and February 2004, the phase III trial enrolled 5611 women with invasive breast cancer and randomly assigned them in a 1:1 ratio to either group 1 (*n*=2807), who received SLN biopsy plus ALND, or to group 2 (*n*=2804) who received SLN biopsy alone (with ALND only if the SLNs were positive). The women were operated on by more than 200 surgeons from 80 centres in Canada and the US. Outcomes analyses were undertaken in patients who were assessed as having pathologically negative sentinel nodes and for whom follow-up data were available.

Altogether 3989 of participants in the study had pathologically negative sentinel nodes. Results show that the eight-year Kaplan–Meier estimates for overall survival were 91.8% (95% CI 90.4%–93.3%) in group 1 and 90.3% (95% CI 88.8%–91.8%) in group 2.

Eight-year Kaplan–Meier estimates for disease-free survival were 82.4% (95% CI 80.5%–84.4%) in group 1 and 81.5% (95% CI 79.6%–83.4%) in group 2.

Additional results show that there were eight regional node recurrences as first events in group 1 and 14 in group 2 (*P*=0.22). The most common adverse events were allergic reactions, mostly related to the administration of the blue dye.

"Our trial shows that overall survival, disease-free survival, and regional control were all statistically equivalent in SLN-negative patients who had an ALND (group 1) or SLN surgery alone (group2)," conclude the authors, adding that results published earlier from the trial have already shown that patient-reported outcomes and morbidity related to range of motion, oedema, pain and sensory defects were lower for the SLN group than the ALND group.

"NSABP B-32 results suggest that when the SLN is negative, SLN surgery alone with no further ALND is an appropriate, safe, and effective therapy for patients with breast cancer," the authors conclude.

In an accompanying commentary, John Benson from the University of Cambridge (UK) wrote, "The paper from Krag and colleagues constitutes a seminal publication on the primary endpoints of loco regional recurrence and overall survival for the largest randomised trial of SLN biopsy. It vindicates contemporary practice of SLN biopsy and provides support for a reduction in extent of axillary surgery for most patients with breast cancer."

However, Benson cautioned that longer follow-up is required, and highlighted the fact that there were almost twice as many regional recurrences in the SLN biopsy only group. "Low volume axillary disease might arguably be clinically relevant if it translates into overall survival differences with longer-term follow-up," he writes.

■ DN Krag, SJ Anderson, TB Julian et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol* October 2010, 11:927-933

■ JR Benson An alternative to initial axillary-lymph-node dissection. *ibid* pp 908–909

Study helps define metastatic breast cancer patients benefitting from phase I trials

➜ British Journal of Cancer

Around one-fifth of patients with metastatic breast cancer (MBC) entered for phase I clinical trials show a measurable benefit after four months, a single-institution UK study has reported.

Despite recent advances in drug development, most women with MBC have a limited median survival time of approximately 18–24 months, with only around 20% alive five years after diagnosis of metastatic disease. Patients who remain sufficiently well may be offered early experimental phase I trials, but appropriate advice for patients remains uncertain due to limited studies documenting outcomes. A recent retrospective analysis reviewing outcomes for patients with MBC participating in phase I clinical trials at MD Anderson Cancer Center (Houston, Texas) found patients had a median overall survival of 6.7 months. In the current study, Charles Swanton and colleagues performed a similar retrospective analysis on MBC patients at the Royal Marsden Hospital (Sutton, UK) entering phase I clinical trials, to further characterise this cohort of patients.

In the study, outcomes for 70 patients with MBC treated between October 2002 and October 2009 in 30 phase I trials in the Drug Development

Unit at the Royal Marsden Hospital were analysed. For those women who had participated in more than one trial, only the first trial entry was considered for the analysis.

Results show that the median overall survival was 8.7 months and the median time to progression was 7.0 weeks. In all, eight women (11.4%) obtained a partial response, 12 (17.1%) had stable disease, and 50 (71.4%) had progressive disease at first radiological assessment. The overall clinical benefit rate (defined as partial response plus stable disease) at four months was 20%.

Patients with triple-negative breast cancer showed greatest clinical benefit rate, at 30.7%, while HER2-positive patients showed a clinical benefit rate of 19% and oestrogen receptor (ER)-positive/HER2-negative patients showed a clinical benefit rate of 8.7%.

In a multivariate analysis, abnormal lactate dehydrogenase levels, serum albumin less than 35mg per 100 ml, more than five previous treatment lines, liver metastases and ECOG (Eastern Cooperative Group) performance status greater than 2 at study entry were significantly associated with poor overall survival. In addition, the multivariate analysis showed that patients treated in trials based on a PARP inhibitor had a significantly longer time to disease progression (Cox regression HR 0.45, 95% CI 0.23–0.86; *P*=0.015). No patients discontinued the trials due to treatment-related toxicities.

"Early patient referral in selected tumour types and chemo-refractory disease may augment the chance of benefit to experimental therapies. In addition, selection of patients based on prognostic tools can assist go-no-go decisions on trial participation for those least likely to benefit," write the authors.

The shorter median overall survival found in the MD Andersen patients, add the authors, probably results from patient heterogeneity and the inclusion of greater numbers of poor prognostic patients.

■ AT Brunetto, D Sarker, D Papadatos-Pastos, et al. A retrospective analysis of clinical outcome of patients with chemo-refractory metastatic breast cancer treated in a single institution phase 1 unit. *Br J Cancer* 24 August 2010, 103 607–612

Advanced GIST patients should remain on imatinib

➜ Lancet Oncology

Interrupting imatinib (Glivec) after three years in responders with advanced gastrointestinal stromal tumours (GIST) leads to a high risk of rapid progression, the BRF14 trial by the French Sarcoma Group has reported.

Imatinib mesylate – a small-molecule inhibitor targeting mutations of the KIT or PDGFRA genes that encode tyrosine kinase receptors – has greatly improved outcomes for patients with advanced GIST, increasing survival from 25% in the era before imatinib to 75% after its introduction. Resistance to imatinib, however, begins to occur after 20– 24 months, due largely to the acquisition of additional mutations.

Since the effect of imatinib discontinuation on progression-free survival and overall survival in long-lasting responders with advanced GIST was unknown, Axel Le Cesne and colleagues, from the Institut Gustave Roussy (Villejuif, France), undertook the current study.

For the open-label, multicentre phase III trial, the investigators identified 50 patients with non-progressive GIST (according to RECIST criteria) who had been taking imatinib 400 mg/day for three years, and randomised them to either continue (*n*=25) or stop taking the drug (*n*=25).

Results show that after a median follow-up of 35 months, two-year progression-free survival was 80% in the continuation group versus 16% in the interruption group (*P*<0.0001). The median time to progression was nine months after randomisation in the treatment interruption group, and had not been reached among the group that remained on imatinib (*P*<0.0001).

All but three patients in the discontinuation group relapsed, most (68%) within a year of stopping therapy. Of the three patients who did not relapse, one had refused to stop imatinib and the other two had their tumours resected.

Among 21 patients in the interruption group with progressive disease, 20 resumed treatment with imatinib at the time of progression. Tumour control (complete response, partial response or stable disease according to RECIST) was obtained in all cases three months after the imatinib re-challenge. Re-introduction of imatinib upon tumour progression in 20 patients was associated with 100% tumour control after three months according to RECIST criteria.

One important issue to be explored was whether imatinib interruption affects the emergence of resistance. Results showed no difference in mutations between the two groups (*P*=0.826).

"Our findings show that imatinib interruption in the setting of advanced disease results in rapid progression in most patients," write the authors, adding that the time to secondary resistance was similar in the two groups. "[This] shows that imatinib interruption neither prevents nor promotes the emergence of imatinib resistance in GIST," they conclude. The absence of any effect of imatinib interruption on overall survival, write the authors, could allow imatinib-free intervals in cases of prolonged and uncomfortable side-effects related to the drug.

They note that similar findings have been reported in chronic myeloid leukaemia (CML), where a pilot phase II trial showed that imatinib interruption resulted in a rapid molecular relapse in 50% of patients judged to be in complete response.

In an accompanying commentary, Michael Heinrich from Portland VA Medical Center (Portland, Oregon), wrote that these findings support the need for continuous treatment with tyrosine kinase inhibitors in GIST, CML and by extension in other cancers responsive to such drugs. "These findings also suggest that current efforts to improve the potency of TKIs against the activated oncogenes in CML and GIST might improve the duration of disease control, but will not be sufficient to achieve a cure," writes Heinrich, adding that therapies with the ability to eradicate the initiating stem cells are needed for a cure.

■ A Le Cesne, I Ray-Coquard, B N Bui, et al. Discontinuation of imatinib in patients with advanced gastrointestinal stromal tumours after 3 years of treatment: an open-label multicentre randomised phase 3 trial. *Lancet Oncol* October 2010, 11:942–949

■ MC Heinrich. Imatinib treatment of metastatic GIST: don't stop (believing). *ibid* pp 910–911