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Education & knowledge through people & facts

Ruth Ladenstein

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A million voices against cancer

Kathy Redmond ■ EDITOR

This September, for only the second time in its history, the United Nations General Assembly will hold a Special Session focused on health. World leaders will gather to discuss the global challenge posed by non-communicable diseases (NCDs) and agree on concise, action-oriented solutions. For those of us concerned about the rapidly growing toll of death and suffering from cancer worldwide, it represents an opportunity that we cannot afford to miss.

Chronic diseases, including cancer, kill more than twice as many people as all infectious diseases, maternal and childhood conditions and nutritional deficiencies combined. They are on the rise, with the largest increases happening in low- and middle-income countries, which are ill equipped to cope with the human and economic toll.

Yet less than 1% of global funding for health goes to support low- and middle-income countries tackle NCDs. One reason is that funds from the biggest global health donors are often linked to the Millennium Development Goals, which don't even mention chronic diseases. Securing a Special UN Session on this topic represents a huge victory for the alliance of international NCD civil society groups, providing a crucial platform to raise awareness about the scope of the problem and force world leaders to focus on identifying workable solutions. Civil society groups will be consulted before the Summit and they will be represented at the Summit. This means that the cancer community will have a voice and can help shape what comes out of it. Individuals, institutions or groups that want to help put NCDs on the global health agenda can visit ncdalliance.org to see how to get involved.

The Union for International Cancer Control (UICC) – the lead cancer organisation within the NCD Alliance – aims to gather one million World Cancer Declaration signatures to present to world leaders at the Summit. Cancer organisations across the world are calling on their members to add their names to send a forceful message to governments and international health policy makers about the cancer community's commitment to take action to stem the tide of cancer. The Maximise Life Global Cancer Campaign initiative, run by the Max Foundation global patient advocacy group, has already secured 13,000 signatures from people in almost 90 countries, showing what can be achieved. In Europe, ESO is joining with other organisations, including ECCO and the European Society for Medical Oncology, to call on everyone who cares about cancer to sign the Declaration.

The World Cancer Declaration details key, affordable actions any country can take that could significantly reduce death and suffering from cancer in a relatively short period of time. We have a unique opportunity to help make sure the global health community gets behind this Declaration and puts cancer at the top of the agenda, where it belongs. So get online at www.worldcancerday.org and make your voice heard!

Ruth Ladenstein:

raising standards of care for our young patients

Marc Beishon

Paediatric oncologists have a well-deserved reputation for collaborating and treating patients within trial protocols, but there are limits to what they can achieve alone. Leading practitioner Ruth Ladenstein is now calling on the EU and member states to commit to improving paediatric cancer care by providing specialist facilities and serious backing for research and data collection.

Of all the cancer specialities, some of the most spectacular gains in outcomes have undoubtedly been in paediatric oncology. Few could argue that an increase to about an 80% cure rate from less than 20% across the range of childhood cancers, albeit over several decades, is not a cause for celebration. Although these cancers are rare, there could be several hundred thousand people in Europe alive today who survived a cancer diagnosis when they were young.

However, as Ruth Ladenstein, president of Europe's Paediatric Oncology Society (SIOPE), points out, this success only highlights the need to maintain and improve the rigorous research environment that led to the gains, as there can be no relaxation of standards, while there are major challenges ahead. Around 15,000 young people, aged 18 and under, are diagnosed with cancer in Europe each year, and at present cure rates more than 3000 will die, making cancer the biggest cause of death in this age group for those above infancy. "We know that when children are treated outside clinical trial settings their outcomes are not nearly as good; survival is on average about 20% worse – a dramatic drop," she says. "And with a new drug in a trial setting we are looking for a 5% to 10% improvement."

This "life-saving factor" should be borne in mind, she says, when considering the impact on patients of the obstacles European Union regulation has placed on conducting trials, and indeed the lack of multidisciplinary paediatric oncology centres able to participate in this sort of research in many countries, particularly in eastern Europe.

"Integration of research and care is a hallmark of paediatric oncology," says Ladenstein, with about 80% of children now treated either in clinical trials or with prospectively monitored therapeutic protocols. But as childhood cancer treatments are firmly in the 'orphan' (more rare) disease category,

RENE VAN BAKEL

thus attracting far less industry funding than the much larger adult cancer field, most of the research is reliant on investigators working in an academic setting, in often complex protocols, mostly with 'off-label' drugs – i.e. drugs that have never been trialled and approved for use in children. The European Clinical Trials Directive has had a dramatic effect on this already fragile research base – an impact even greater than in the adult tumour area.

"We estimate that the number of new trials has gone down by 70% since the implementation of the directive as there is just so much more funding and time now needed to deal with issues such as ethical committees around Europe and insurance in trials deemed to be high risk. Meanwhile we have virtually no funding or interest in running studies on existing off-label drugs, and these are classed in some countries as investigational medical products, which further adds to the administrative burden if we need to use them in trials. And of course because paediatric cancers are uncommon we do need multicentre, multicountry studies to accrue sufficient patient numbers."

As she adds, just as in adult cancer, the era of chemotherapy has largely run out of steam at the paediatric level, and the pursuit of translational research and new biological therapies is especially demanding for academic investigators short of funds. Then there is the paradox that this branch of oncology also contains – or should do – the most neglected group in cancer, namely teenagers and young adults. And all children with cancer need the major commitment of follow up through much of their lives to monitor the effects of treatment.

There are also urgent needs for gathering much better epidemiological data from various countries, for fostering multidisciplinary standards of care and for getting patients and families more involved in pressing for research. It's a huge agenda by any measure.

Ladenstein speaks from long-standing involvement in the paediatric oncology research community, specialising in neuroblastoma, and having spent her career working up to head the solid tumour unit at St Anna Children's Hospital in Vienna, Austria, and also holding an associate professorship at the University of Vienna. The St Anna Kinderkrebsforschung (children's cancer research institute) has long been a research hub in the German-speaking region and internationally, but it has really been put on the wider map with two recent EU initiatives that Ladenstein hopes will help to unravel the 'red tape' that she believes could seriously hold back progress in her speciality.

The first, now ended, was 'Overcoming cancer with research', a two-year communications project that aimed to raise public awareness of childhood cancer research. This media project, for which St Anna was the coordinating organisation, working with the German Childhood Cancer Foundation as a partner, has produced a comprehensive website (www.overcomingcancerwithresearch.eu), a film (Little Heroes – Great Opportunities), press conferences and other activities.

It also provides details of various paediatric research networks and other projects that have EU funding. One of these is ENCCA (European Network for Cancer Research in Children and Adolescents), a major €12 million initiative under the EU's 7th Framework Programme, for which Ladenstein is the coordinator. "It is a four-year project that started this year and our aim is nothing short of building a sustainable Europe-wide virtual institute that will unite the paediatric oncology community," she says.

Meanwhile, she adds, disparities in care standards are being addressed by SIOPE, which has drawn up 'European Standards of Care for Children with Cancer' for paediatric oncology, and a 'seven-point plan' for delivering the overall agenda (see p9), including a call for all member states to have national cancer plans that contain specific

"Children are wonderful patients to be with – they understand a lot when you explain properly"

standards for age-appropriate treatment and care for children and adolescents with cancer.

It's a familiar story in European oncology: many interest groups have realised recently that there is much to be gained by combining the efforts of national societies and institutions to gain scale for research and to lobby and network more effectively at both European and state levels. As Ladenstein adds, "While there has been effective networking in childhood cancer – indeed more so historically than in most adult tumours – efforts have largely been focused on specific diseases such as neuroblastoma."

Now it's vital to unite research networks and lobbying work, she believes, and Ladenstein finds herself at the head not only of one of oncology's most important European societies, but also a key project in ENCCA, given the impact it could have on issues such as the Clinical Trials Directive.

Her path into medicine was almost preordained – "It was what I wanted as a little girl" – and she found herself drawn to paediatrics despite a conscious choice to resist it, as she felt women too often find themselves earmarked for the speciality. "But I loved it," she says, "and I did all my standard paediatric training at St Anna. In fact despite moving into oncology I'm still a practising general paediatrician, as when I'm on call in the hospital I see all children, not just those with cancer."

It was early in her career when her chief, Helmut Gadner – one of the pioneers of the BFM (Berlin-Frankfurt-Münster) leukaemia protocols developed in Germany, who recently retired from St Anna – pointed her in the direction of oncology. "We had just started to treat children with cancer then, and he gave me a paper to study on sarcoma patients, and from that we started the first Austrian sarcoma study."

Ladenstein says that far from childhood cancer being a daunting area, "it's exciting because we have a 40% better chance of curing them than we do with adults. Some types of paediatric tumours respond much better to chemotherapy and children are wonderful patients to be with. They understand a lot when you explain properly and it makes them mature in a very short time. It's a pleasure to be with them and their families at a critical time, and now I also see them as grown-ups with their own children." But of course there is great sadness when treatment fails in some. "I especially feel for teenagers – you should never die when you have hope for the life ahead of you."

As she adds, it is the right place to be for those who want to be rewarded in terms of outcomes and scientifically. "We are on the edge of a fast-moving field and there is so much research to be done."

Needing more research experience herself, and the recipient of an Austrian award, Ladenstein cast around for a project abroad, landing in Lyon, France, at the Léon Bérard Centre. France has been a European cradle of paediatric oncology, and she was quickly immersed in analysis of data on neuroblastoma transplants, and also on Ewing tumours and lymphoma patients around Europe. She also studied mechanisms in neuroblastoma cells in the laboratory, and went on to work and study further in Paris.

Neuroblastoma is the most common childhood solid tumour outside of the brain, and the most frequent of all under the age of five – in fact it is the second most common cause of death in children after domestic accidents. As a neuroendocrine disease it often develops from the adrenal glands. Ladenstein explains that it also has a wide spectrum of risk, and stem cell transplants are given after high-dose chemotherapy treatment for overcoming tumour cell resistance in the more severe cases. But low-risk disease often regresses to a benign state without any treatment, and identifying how best to apply high-dose regimens became a particular goal for her following her return to Austria.

"It is one of the most fascinating of cancers because it is completely driven by tumour biology, as we have been discovering," says Ladenstein. "We

"It's very hard when parents read about our trials and ask why we can't give these drugs to all children"

have learnt that neuroblastoma in infants can even regress from the metastatic stage and does not need chemotherapy, unless there are specific risk factors that do require intensive treatment. So far we know half of patients need little or no chemotherapy and can be spared high-dose treatment, and we have improved outcomes in the high-risk group from 20%–35% to more than 50%, which is quite an achievement. It is knowing early on who has an unfavourable profile that improves outcomes."

Ladenstein has been at the centre of both local and Europe-wide neuroblastoma research that has found prognostic markers for risk and developed new treatments and protocols, and she is the co-ordinator of the SIOP European Neuroblastoma Research Network (SIOPEN-R-NET) and chair of SIOPE's neuroblastoma group (the research network was funded by the EU's Fifth Framework Programme, but continues to operate today). "The history of paediatric oncology is that we run one protocol after another and make slight progress by optimising treatment plans over many years, but we have learnt so much more now about prognostic markers, stratified treatment and biology in most child tumour types.

"In neuroblastoma, a key focus now is still on the high-risk group and we have a huge trial running that has accrued more than 1500 children across 20 countries and we are getting exciting results from the randomisation, which we will be taking to the ASCO conference in the US this year. We will show that a European protocol we have developed is performing better than the best American standard."

She says the Children's Oncology Group in the US had demonstrated a significant improvement for neuroblastoma immunotherapy using a monoclonal mouse-human chimeric antibody (ch.14.18). The SIOPEN group then undertook to provide access to this antibody for neuroblastoma patients in Europe via the trial, but this work illustrates well the difficulties that paediatric oncologists face in pursuing new treatments.

It involves the production and distribution for clinical testing of this 'chimeric' (combination) antibody for use in the high-risk trial – but so far this is an entirely academically driven effort, with all that means for pressure on funds to bring a new drug to market. "It is very unusual for us to attempt drug development without industry support – but we have obtained about €2 million through our own fundraising efforts. Even so, we only have a limited amount of the drug for the controlled trials, and we are hoping to find an industrial partner and also greater government support for drug production, especially in the UK, so we can open up more trials."

She also mentions another drug that could improve outcomes when given in combination, by promoting white blood cell production, which is being used in trials in the US, but is simply not available in Europe. "We eventually tracked down a potential 'importer' supplier in Switzerland, but the pharmaceutical licence holder wasn't interested in making it available," says Ladenstein. "It's very hard when parents read about our trials and ask why we can't give these drugs to all children. I have to explain we are not a drug company, that the drugs aren't mature enough yet to be on the market and there can be concerns about toxicity, and simply that we do not have enough of them, such as the chimeric antibody, and we are not allowed to offer the drug outside a controlled trial setting."

The antibody in question was first researched some 20 years ago for adult and childhood cancers, but as Ladenstein points out, children in Europe have been "extremely poorly served" in access to innovative drugs that have been investigated and developed for adults. She is encouraged, however, by a recent initiative that could help children gain better access to new drugs, namely the requirement for pharmaceutical companies to develop paediatric investigation plans (PIPs) for new adult drugs, where appropriate, under the recent EU Paediatric Medicine regulation, which also aims to promote safe and effective treatments in general.

HOW WELL DOES YOUR COUNTRY SERVE ITS YOUNG CANCER PATIENTS?

SIOPE has drawn up this seven-point plan as a guide for policy makers on how to upgrade paediatric cancer services.

1. Cancer plans. Every country should have a national cancer plan that contains specific standards for age-appropriate treatment and care for children and adolescents with cancer.

2. Registries. Every country should support prospective registration of new cases and outcomes of all cases using the International Childhood Cancer Classification scheme, extended to include adolescent cases.

3. Access to specialists. Every country should have defined referral pathways so that each patient is managed at an age-appropriate specialist treatment centre that works within a national or cross-border network structure and can have access to innovative therapies in development when needed.

4. Multiprofessional teams. Every child and adolescent with cancer should be treated by a multiprofessional team which has a sufficient volume of activity to maintain expertise and which participates in audit and accreditation schemes.

5. Specialist training. Specialist training in paediatric haemato-oncology should be recognised in every European country.

6. Family support. The crucial role of parental/family support should be recognised as critical to treatment outcome and survival of the young cancer patient.

7. Research. Greater EU and national support is needed for investigator-led clinical and translational research, to reverse the recent decline in participation in clinical trials, which, to date, has greatly benefited the development and delivery of 'best practice' of care for young people with cancer.

The benefits, however, won't be felt for a long time, she says. "We may see an impact from the crossover from adult drugs in 10 to 20 years time. There are only a few that are ongoing at present, but it is a move in the right direction." The regulation also fails to resolve the major problem of getting approval for drugs that are already widely used off-label. "There is not yet any investigational process or funds for us to do this."

About 80% of drugs used in paediatric oncology are used off-label, and even those that are approved are not often labelled appropriately for certain age groups in terms of dose calculation, for example. "We need to take steps to ensure all the drugs we use for children are safe and effective – but despite a backwash of 30 years of clinical trials we still have this huge burden of off-label drug use and barriers to moving forward, such as the continued classification of many of our drugs as investigational medical products in some countries, despite their long use." If drugs are treated as investigational, they require 'expedited' reporting to the European Medicines Agency, EMA, and Ladenstein fears that much of these data, which could be valuable for knowledge about say toxicities in multiagent trials, are disappearing into a 'black hole'.

There are funds available from the EU's Framework Programmes for drug development that could help investigate the pharmacokinetic/dynamic behaviour of off-label drugs in children and so move towards approval, but as Ladenstein points out, the only way for academics to access these funds is to compete against one another, which means many will simply waste a lot of effort writing applications.

"We need dedicated funding to investigate the older drugs we use, and there is a feeling that some should be entered into randomised trials, which would be very costly. However we do need to charge experts to do the work on correlating drugs properly in terms of their behaviour with the course of a disease and the dose, as clearly children are different

"We could certainly aim now to get that 80% off-label figure down to 40% in five years' time"

"It took 30 years to see the higher incidence of breast cancer in those treated for Hodgkin's lymphoma"

from adults. We could certainly aim now to get that 80% off-label figure down to 40% in five years' time." If standard chemotherapy protocols can be optimised, Ladenstein says that adding new drugs could then add another 10% benefit in outcomes.

Lobbying from SIOPE will continue on this issue, as it is not explicitly part of the work programme for ENCCA. "In the new project, though, we will be aiming to influence the Clinical Trials Directive so it is more feasible for paediatric oncology, such as by developing a contract framework that allows academic institutions to become coordinating pan-European trial sponsors, delegating tasks to national bodies so we can share the burden. We are also looking to use a not-for-profit insurance organisation, maybe insuring studies through national health services." (Both Ladenstein and the previous SIOPE president, Kathy Pritchard-Jones, have written about the absurdities of the Clinical Trials Directive, which include the stipulation that crushing tablets in trials to enable children to swallow drugs is not allowed as it is deemed a 'manufacturing' process – *EJC* 44:2106–2111.)

The clinical trials work package of ENCCA (just one of 18 'work packages' tackling various challenges in paediatric oncology) will also aim to streamline childhood cancer trials by using standard templates and datasets; determining just what an investigational medicine should be; and cutting duplication and fragmentation by promoting more multinational trials.

"In other work packages we want to explore how we can build better registry data for childhood cancers, and how we can improve long-term survivorship as children grow up to become adults, by following up late-effects of treatment. One idea is for them to carry a survivor's passport that contains updated information and is always with them. Another project is PanCare, which focuses on long-term effects. The challenge is that this is not like caring for those with just diabetes or a heart condition – we will still need multidisciplinary teams throughout."

It seems from existing data that paediatric cancers are not increasing in overall incidence, but if national registries improve, Ladenstein says, trends in certain tumours and leukaemias may become apparent at a European level. At present, she adds, only localised events such as Chernobyl and other pollution in some countries appear to have given rise to higher than usual rates of childhood cancers. "We also need very long observation times concerning treatment – for example it took 30 years for us to see the higher incidence of breast cancer in those who had been diagnosed with Hodgkin's lymphoma and had been given certain drugs and radiotherapy."

The biggest work package, in terms of 'person months', is on networking among preclinical research groups to create common data sharing and bio-information tools, and Ladenstein notes that an overall aim of ENCCA is to bring researchers together across the range of paediatric cancers, to possibly identify shared biological pathways, for example.

More funding is likely to come from pressure from advocacy groups, she believes. "SIOP [International] has a committee working with the International Confederation of Childhood Cancer Parent Organisations, which can be a strong voice for us. I know from speaking to people at the US National Institutes of Health that funders are driven much more by parents than by doctors."

She hopes that SIOPE will benefit from increased membership as a result of ENCCA, as people recognise the importance of integrated working. The European branch of the society has around 900 members and could do with more interest from national organisations, but Ladenstein says there is difficulty in getting people to commit to additional membership fees. "But we have a strong European agenda that ENCCA will increase further – and I hope it will show people what they are missing."

SIOPE is a founder member of ECCO and runs a paediatric stream at the conference. It joins

the SIOP International congress when it convenes outside Europe (this year it will be in New Zealand). But as Ladenstein adds, it is important that networking continues in countries that are most underrepresented in membership and that have more trouble meeting standards of care, such as in eastern Europe. "SIOPE has a partnership with the national society in Poland, and we jointly drew up the European Standards of Care for Children with Cancer," she says.

A survey of the state of regulations and standards of children's cancer care in 27 European countries conducted in 2008 by Jerzy Kowalczyk, of the Children's Hospital in Lublin, Poland, revealed that only Austria, Belgium, France, Germany and Italy had officially recognised regulations in place, with the most comprehensive in Germany.

SIOPE's European Standards of Care, which were developed from this, are described by Ladenstein as guidelines on the minimum requirements for bringing children and families through intensive treatment, "on factors such as access to drugs and protocols, sufficient team members, how children are looked after in the wider context such as schooling, and so on."

Given the importance of trials and protocols for best outcomes in paediatric oncology, having dedicated cancer centres for children is also critical, adds Ladenstein, but it can mean travelling and staying a long way from home. And at primary care level, those countries that have paediatricians who see children as they grow up are also in a better position than those where children mainly see general practitioners.

"You need a lot of expertise with children to suspect the symptoms of cancer early on. For example, a child needs to be undressed completely to see possible swelling associated with neuroblastoma, which would more commonly be attributed to a condition such as gastroenteritis. Similarly, tiredness and swellings can be associated with leukaemia. These are things I teach my university students in basic oncology classes. I do feel that children should be looked after by paediatricians throughout their childhood and not just referred to specialists."

She has been fortunate, she adds, to have worked with mentors such as Gadner in Vienna and Thierry Philip in Lyon, and notably Olivier Hartmann at the Institut Gustave Roussy in Paris, "a fantastic personality", who died in 2009.

Despite her workload, Ladenstein, who has a teenage daughter, has many hobbies, including mountain hiking, sailing, diving and ballroom dancing. She may need all her nifty footwork skills in dancing the tango with the powers that be to achieve the establishment of the European virtual institute for paediatric oncology, which is one of key aims for the next few years.

"Having dedicated cancer centres for children is critical, but it can mean staying a long way from home"

Treatment of triple negative breast cancer

Triple negative breast cancers, as a subgroup, are associated with a poor prognosis. But different subtypes within triple negative disease are associated with different outcomes, and they also differ in the way they respond to different treatments. Here Angelo Di Leo provides an overview of what is currently known and the questions being addressed by ongoing clinical trials.

In treating triple negative breast cancer, the first thing is to ensure the diagnosis is correct – it is essential to correctly evaluate oestrogen receptor (ER), progesterone receptor (PgR) and HER2 in primary tumour samples to eliminate 'false' triple negative tumours. The ALTTO trial, which is testing lapatinib and trastuzumab in the adjuvant treatment of HER2-positive breast cancer patients, included central pathology review for ER, PgR and HER2 status. Results showed discordance in 4%–16% of cases between the evaluation of ER, PgR and HER2 in local laboratories and the central laboratory (personal communication, Giuseppe Viale, European Institute of Oncology, Milan).

This is a serious issue because adjuvant therapy decisions are largely guided by these biomarkers. Good communication between oncologists and pathologists is essential to try to reduce such discordance.

Another important consideration is that not all triple negative tumours have a bad prognosis. For example, a retrospective study of 13 International Breast Cancer Study Group adjuvant

European School of Oncology
e-grandround

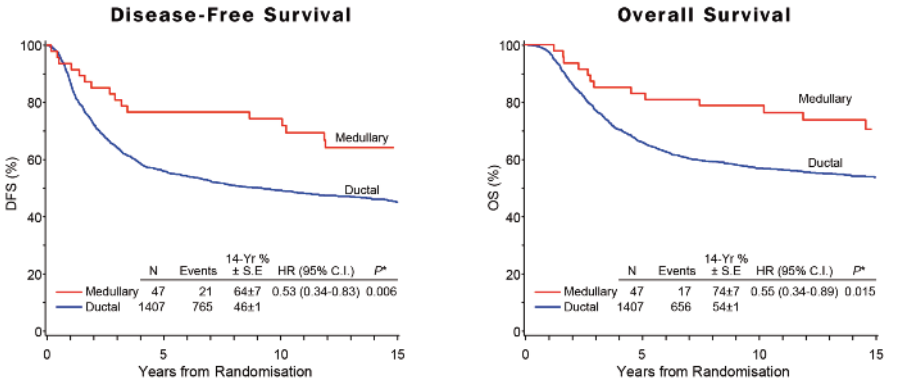
The European School of Oncology presents weekly e-grandrounds which offer participants the opportunity to discuss a range of cutting-edge issues, from controversial areas and the latest scientific developments to challenging clinical cases, with leading European experts in the field. One of these is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

In this issue, Angelo Di Leo of Sandro Pitigliani Medical Oncology Unit, Prato Hospital, Italy, reviews the challenges of managing triple negative breast cancer, including the biological heterogeneity within the subgroup that can impact on clinical outcomes, the clinical trial evidence with cytotoxic agents and emerging data with PARP inhibitors.

Lisa Carey, of the Lineberger Comprehensive Cancer Center, University of North Carolina, United States, poses questions sent in by participants during the live presentation. The e-grandround was summarised by Susan Mayor.

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

NOT ALL TRIPLE NEGATIVE TUMOURS ARE BAD



A pooled retrospective analysis of 13 adjuvant trials showed high-grade, ER-negative breast cancers vary markedly in outcome depending on whether they are of medullary or ductal subtype

Source: Huober et al. (2010) *JCO* 28 (suppl 15): abstract 630

trials reported at ASCO 2010 identified patients with ER-negative, grade 3 early breast cancer and compared outcomes for central pathology laboratory confirmed medullary cancers (n=47) and ductal infiltrating cancers (n=1407). Despite high grade and ER negativity, patients with medullary tumours had less vascular invasion, better disease-free survival and better overall survival compared with those with the ductal subtype (see above).The better prognosis for the medullary subtype should be considered in treatment decisions.

Sensitivity to cytotoxic agents

Anthracyclines

Anthracyclines have been used to treat breast cancer for many years. Triple negative tumours may have proliferation-driven overexpression of the anthracycline drug target topoisomerase II (topoII) alpha and impaired DNA repair due to BRCA1/2 dysfunction. As such, this subgroup might be particularly sensitive to treatment with anthracyclines.

Preclinical data support the concept of increased activity for topoII inhibitors in tumours carrying BRCA1/2 dysfunction. In a cell line model, the topoII inhibitor etoposide was administered to BRCA1 wild type and BRCA1 deficient breast cancer cells, and BRCA2 wild type and BCRA2 deficient fibroblasts. Differential cytotoxicity was observed based on BRCA status with greater cytotoxicity in cells with BRCA loss (see opposite, *top graphs*). The same cell lines were pretreated with aclarubicin at low dose to block the topoII binding site without causing cell death, then re-treated with etoposide. This resulted in markedly reduced etoposide cytotoxicity and elimination of any differential BRCA effect (see opposite, *bottom graphs*). This highlighted that topoII-inhibitor-induced DNA damage is predominantly mediated by topoII binding rather than direct DNA binding.

In addition, an exploratory planned event-free survival analysis by four molecular subgroups (defined using ER, PgR, grade, HER2) reported at ASCO 2010 looked at five adjuvant clinical trials comparing anthracyclines with CMF (cyclophosphamide, methotrexate, 5-fluorouracil) in the adjuvant treatment of early breast cancer. Results showed no clear superiority of anthracyclines over CMF in the so-called highly hormone sensitive tumours, while anthracyclines appeared to be better than CMF in moderately hormone sensitive, HER2 amplified and triple negative subgroups. Notably, anthracyclines seemed to be more active than CMF in the triple negative subgroup (see p16).

These data have not been confirmed by other groups, but this is the largest dataset to date looking at these different subtypes. At ASCO 2009, contrasting results were presented in the exploratory subgroup overall survival analysis of the Canadian NCI-MA5 trial comparing anthracycline-based therapy versus CMF. In this analysis, CMF was favoured over anthracyclines in the core basal triple negative subgroup.

Retrospective and underpowered clinical data are interesting but conflicting, and as such cannot be translated to current clinical practice. More data are required from larger studies.

Summing up this section, cell lines and molecular pathology data suggest that triple negative ductal infiltrating carcinoma may have increased sensitivity to anthracyclines. Clinical data from retrospective studies with limited statistical power are controversial. While we wait for more data – ideally from prospective studies – anthracyclines should still be considered an important component of chemotherapy regimens for triple negative tumours.

Question: *You talked about medullary cancers, and what you called 'false' triple negative tumours. Can you expand on the different categories of prognosis separate from medullary and other triple negatives?*

Answer: *This is an important point. My impression is that we have slightly ignored the heterogeneity in the histology of triple negative tumours. Beyond ductal carcinoma, there are also medullary, apocrine and squamous cell carcinomas which are also triple negative. Based on retrospective data and not on prospectively designed studies, my impression is that these different subtypes may need a different treatment approach. Medullary tumours have better outcomes than infiltrating ductal triple negative carcinomas. So I think we should make an effort – ideally a collaborative effort – to gain more knowledge about the treatment and prognosis of the uncommon subtypes.*

Question: *One of the things that strikes me about patients with triple negative breast cancer when they come to the clinic is that they are convinced they have a poor prognosis, no matter what. It might be interesting to remind readers that disease-free survival at five years for triple negative breast cancer of conventional types is 85%, so many patients can do quite well.*

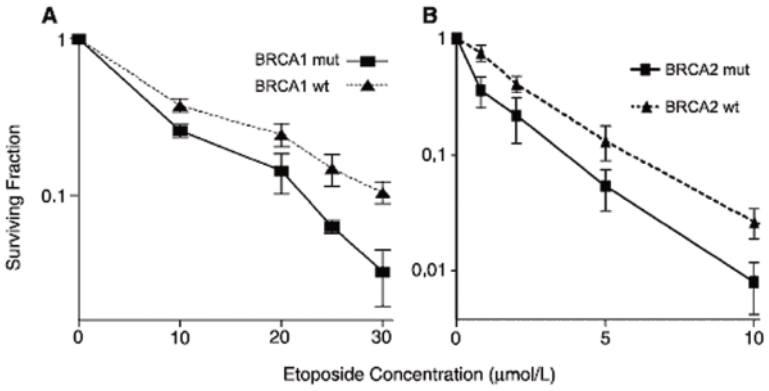
Answer: *When patients know they have triple negative status, they are often terrified, independently of whether they have medullary or ductal infiltrating carcinoma. I think it is our task to explain to patients that this is a disease in which there is heterogeneity in terms of outcome, even though these tumours are all characterised by triple negative status.*

Platinum compounds

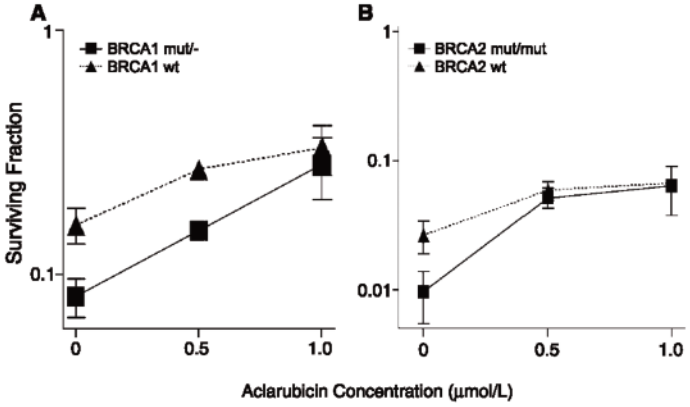
Four neoadjuvant, single-arm trials have been reported with platinum compounds in triple negative breast cancer, in which patients were treated with cisplatin alone or in combination. Results showed pathological complete response (pCR) rates ranging from 15% to 72%. It is particularly important to note results from a small study reported at ASCO 2009 (Gronwald 2009, abstract 502) of 25 patients showing a remarkably high, 72%, pCR rate with neoadjuvant cisplatin. Interestingly, this is the only study in which patients were selected according to the presence of BRCA1 mutation. This is an important signal, which seems to suggest there can be extraordinary activity with cisplatin if patients are selected according to the presence of BRCA1 dysfunction.

BRCA1/2 DEFICIENT CELL LINES RESPOND MORE TO TOPOII α INHIBITORS

BRCA1 deficient breast cancer cells and
BRCA2 deficient fibroblasts exposed to etoposide



Etoposide 25 µmol/L in presence of low dose
topoII α inhibitor (aclarubicin)



Preclinical data show that DNA damage and cytotoxicity from topoII inhibitors is greater in BRCA deficient cells (top) and that cytotoxicity is mediated indirectly by topoisomerase binding, rather than direct DNA binding (bottom)

Source: Treszezamsky et al. (2007) *Cancer Res* 67:7078–7081

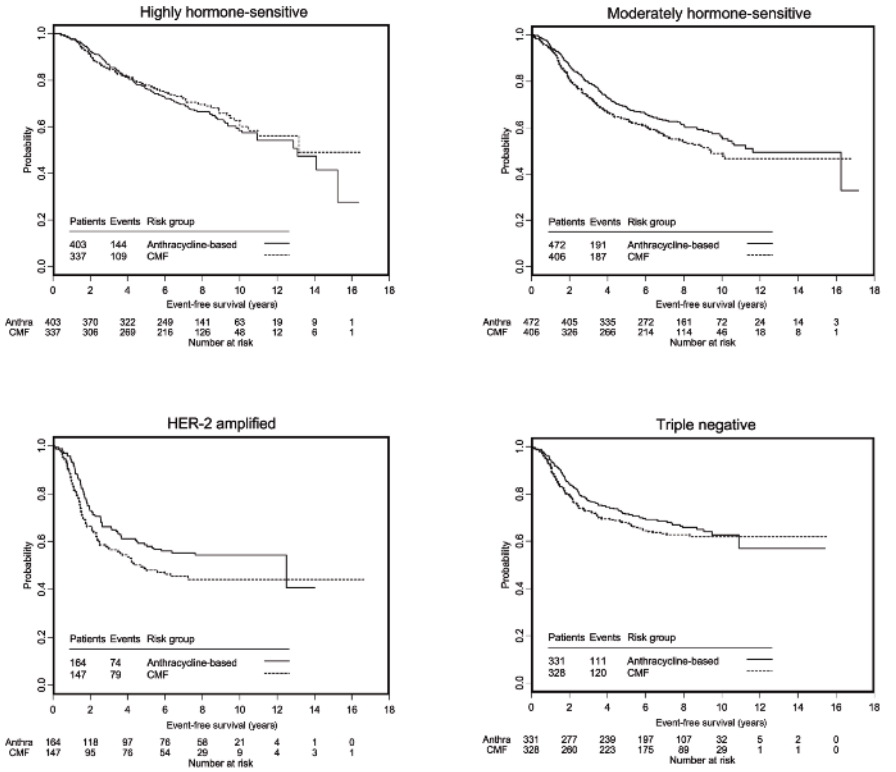
A single-institute phase II trial with cisplatin in triple negative advanced breast cancer was reported at ECCO/ESMO 2009, in which 126 patients pretreated with first-line chemotherapy were randomised to metronomic (repetitive, low doses) oral cyclophosphamide and methotrexate with or without cisplatin. Results showed better outcomes in patients treated with cisplatin: CR 8% vs 5%; PR 55% vs 28%; median time to progression 13 vs 7 months; median overall survival 16 vs 12 months (Bhattacharyya et al. *Eur J Cancer* 7 (3 Suppl):18). This gives further evidence for efficacy of cisplatin in triple negative breast cancer, but more data are needed.

Another study randomised patients with metastatic triple negative breast cancer to cetuximab followed by cetuximab plus carboplatin on progression, or to cetuximab–carboplatin (*JCO* 26: abstract 1009). Results showed higher overall response rate when the combination was used initially (17% vs 6% with cetuximab alone) and greater clinical benefit (31% vs 10% with cetuximab, and 25% for the two drugs used sequentially).

The first-line TNT trial, from King's College London, in patients with centrally confirmed triple negative advanced breast cancer is underway to compare four treatment arms: platinum, platinum plus PARP inhibitor, docetaxel, and docetaxel plus PARP inhibitor. Patients may cross over at progression (personal correspondence, Andrew Tutt, King's College London). I think this trial will fully address the issue of platinum compounds in triple negative advanced disease.

We are also starting a phase II randomised study in Italy comparing a non DNA damaging regimen (capecitabine plus oral vinorelbine) with a DNA damaging regimen (cisplatin plus cyclophosphamide). The triple negative status is

ANTHRACYCLINES VS CMF IN DIFFERENT SUBTYPES



An exploratory (planned) analysis of four adjuvant clinical trials showed that certain subtypes of breast cancer, including triple negative tumours, are more sensitive to anthracyclines than to the CMF regimen

Source: Di Leo, presented at ASCO 2010, abstract 519

defined not from the archived primary tumour sample but in real time from circulating tumour cells. Non-triple negative patients are also being treated in this trial, providing a control arm to demonstrate that the superiority of a DNA damaging regimen occurs predominantly in triple negative disease.

Predicting sensitivity to DNA damaging regimens

Several studies have been conducted to identify molecular markers of sensitivity to DNA damaging regimens. A Japanese study in 60 patients with early disease treated with neoadjuvant epirubicin/cyclophosphamide followed by docetaxel assessed DNA repair proteins on tumour samples at baseline and 18–24 hours after chemotherapy. The panel of DNA repair proteins assessed by immunohistochemistry included BRCA1, Rad 51, γH2AX, and conjugated ubiquitin (all at baseline) and Rad 51 (post treatment). These proteins are all involved in homologous recombination, which is a key mechanism of repair of double-strand DNA breaks induced by anthracyclines. DNA damage response score was assessed from 0 to 4, with the highest score reflecting the greatest efficacy in DNA

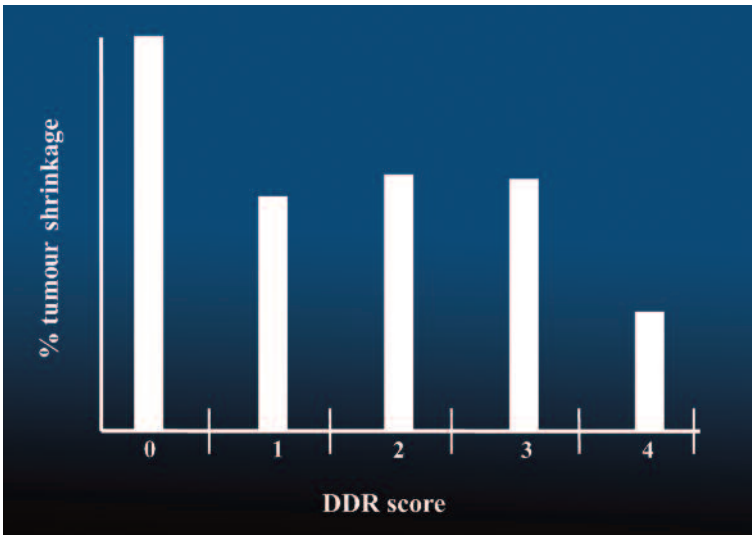
repair (Asakawa et al. *Breast Cancer Res* 12(2):R17). The DNA response score showed an inverse correlation with tumour shrinkage and response rate. The lowest score was associated with the highest efficacy (see below). These data are very interesting, but very preliminary.

The Comet assay is a potential tool for identification of DNA damage and prediction of sensitivity to DNA damaging therapy. Different chemotherapy agents can cause DNA strand breaks leading to DNA fragmentation. This fragmentation can be measured using Comet, a test commonly used in toxicology, in which cell scrapings are taken from fresh primary tumour and corresponding non-cancer tissue. Cells are layered on agarose pre-coated slides. Single gel embedded cells are lysed to isolate nucleoids containing supercoiled loops of DNA. Labile DNA at sites of damage is able to unwind and migrate differentially out of the cell during electrophoresis. When observed by fluorescence microscopy, cells with DNA damage resemble comets with a nuclear head and 'tails' of fragmentation (see p18). The comet tail in cancer cells are due to DNA fragmentation, while healthy cells show no DNA fragmentation.

Software linked to the microscope measures comet tail length and tail intensity for each cell, and calculates average values for each sample. The tumour sample Comet score is then adjusted by comparison to the non-tumour sample score (*Mol Biotechnol* 26:249–261). The non-tumour sample can have some DNA damage that is induced by tissue sampling, so it is very important to adjust for this.

In our pilot study of 91 patients with early breast cancer classified by molecular subtypes (highly endocrine-sensitive, moderately endocrine-sensitive, HER2 positive, triple negative), results showed no substantial differences in Comet scores by subtype. However, the triple negative subgroup had the largest inter-patient variation. There was also substantial intra-tumour heterogeneity in Comet scores, suggesting some areas of a tumour have substantial dysfunction in DNA repair while others do not. Intra-tumoural heterogeneity in DNA repair and presumed heterogeneity in sensitivity to DNA damaging agents may in part offer a biological rationale for resistance to DNA damaging therapy.

TUMOUR SHRINKAGE BY DNA DAMAGE RESPONSE SCORE



Epirubicin–cyclophosphamide given neoadjuvantly led to greater shrinkage in tumours with a low DNA damage response score (DDR)

Source: Asakawa et al. (2010) *Breast Cancer Res* 12(2):R17

Summing up this section, data from phase II non-randomised trials in the neo-adjuvant setting suggest that triple negative tumours carrying BRCA1/2 dysfunction might be highly sensitive to platinum compounds. Data from phase II and phase III randomised trials are still preliminary but are not against the hypothesis that triple negative tumours have increased sensitivity to platinum compounds. Ongoing studies are attempting to identify molecular profiles and biological features predicting response to DNA damaging cytotoxics.

PARP INHIBITORS

PARP inhibitors potentially provide a targeted therapy approach for patients with triple negative disease. A tumour with dysfunction in BRCA and dysfunction in PARP may lack two important DNA repair mechanisms: the base excision repair mechanism, which is mainly dependent on PARP, and homologous recombination, which is mainly dependent on BRCA1/2. Inactivation of these two pathways may lead to endogenous cell damage and increased sensitivity to DNA damaging chemotherapy, radiotherapy and other agents that damage DNA.

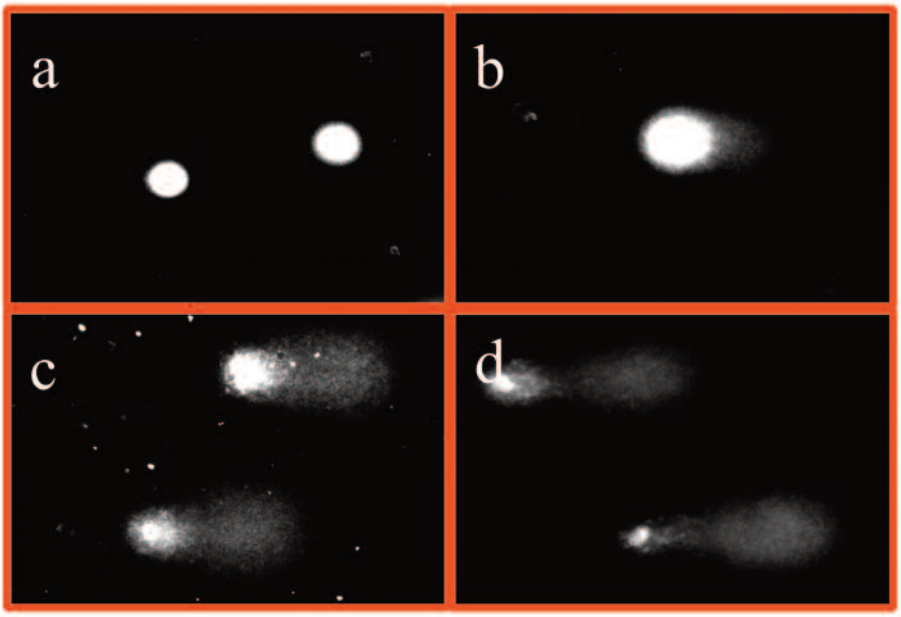
In triple negative breast cancer, homologous recombination may be inactivated due to BRCA1 dysfunction, with compensatory upregulation of PARP activity and the base excision repair pathway. If you then give a PARP inhibitor, you will also inactivate the base excision repair mechanism.

Cell death due to loss of these two pathways is called 'synthetic lethality'. This is the rationale for the use of PARP inhibitors in cancers carrying BRCA1 dysfunction, and also for the combination of DNA damaging chemotherapy with PARP inhibitors.

Several PARP inhibitors are being evaluated in clinical trials. The most advanced data on PARP inhibitors were reported recently in *The Lancet* by Andrew Tutt and colleagues (vol 376, pp 235–444). This international study was undertaken in BRCA-mutated patients with advanced, heavily pretreated breast cancer, in which all patients were treated with the oral PARP1 inhibitor, olaparib (400 mg twice daily or 100 mg twice daily). Both doses showed activity in this heavily pretreated population, with the 400 mg dose showing a higher overall response rate of 41% compared with 22% for the 100 mg dose. Some toxicity was reported, with the main grade 3–4 side-effects being fatigue, nausea, vomiting and anaemia. Olaparib appears to be tolerable, with manageable toxicity.

Other data come from a randomised phase II trial with the parenteral PARP inhibitor iniparib (*NEJM* 364:205–214). Patients had triple negative metastatic breast cancer, but dysfunction in BRCA1 was not considered in the eligibility criteria, as it was for the olaparib study. One hundred and twenty patients participated in this study. Most had received one or two prior lines of treatment for metastatic disease. The control arm was gemcitabine plus carboplatin and the experimental arm was the same chemotherapy plus iniparib. Results showed a higher rate of clinical benefit in the iniparib arm (55.6% vs 33.9%, P=0.015), with longer progression-free survival (5.9 months vs 3.6 months, P=0.012) and overall survival (12.3 vs 7.7 months, P=0.014). This phase II randomised study was the basis for moving to the phase III study, with the same therapy arms, that has recently completed accrual in the US. Results should become available in the coming year.

PREDICTING SENSITIVITY TO DNA DAMAGING AGENTS



The Comet assay distinguishes healthy cells (a) from cancer cells, which have a comet-like tail indicating DNA fragmentation (b, c, d)

Source: Galardi et al., presented at the IMPAKT Breast Cancer Conference, Brussels, 2010

Remaining questions with PARP inhibitors

We have a lot of data on PARP inhibitors, but we also have many questions about their optimal use in breast cancer patients. It is important to understand whether there are differences in activity between continuously administered oral agents and intermittently administered IV agents. This might have implications in terms of the degree of inhibition of the PARP enzyme.

Other questions include: What are the best cytotoxic partners for these compounds? What is their activity in non-triple negative disease, particularly in those displaying some dysfunction in DNA repair? Are there molecular predictors of response to PARP inhibitors as well as to DNA damaging agents? What is the long-term safety of these compounds? This last question is extremely important, particularly because we are already looking at evaluating these compounds in early disease.

Three studies further evaluating PARP in triple negative disease are:

- The UK-led NeoBIG trial. This will test iniparib in combination with docetaxel or carboplatin/gemcitabine in the neoadjuvant setting.
- The BIG trial, co-ordinated by the International Breast Cancer Study Group. This will test iniparib in combination with epirubicin in the first-

Lisa Carey, from the Lineberger Comprehensive Cancer Center, University of North Carolina, USA, hosted a question and answer session with Angelo Di Leo.

LC: *The last section focusing on PARP inhibition is probably one of the most exciting areas. We have one phase II trial, but I think it is also worth noting that there were triple negative cancers that do not carry germline BRCA mutations, and there have been some phase II trials using various agents that have not been so exciting. This is obviously an area to be determined in a number of trials moving forward.*

Could you expand on long-term safety? There is so much enthusiasm for these drugs that if they do turn out to be positive in the phase III setting, I think people may use them quite widely. You commented a little about your concerns in the adjuvant setting.

AD: I think this is an interesting field of research. The concern is related to potential secondary tumours, leukaemia and myelodysplastic syndrome, particularly when these agents are used in combination with DNA damaging agents, specifically anthracyclines. This is an issue that needs to be clearly explored. Differential PARP inhibitor effect in tumour and healthy cells might suggest that we will not see any long-term safety concerns, but this is an issue that will have to be carefully evaluated in future-generation adjuvant therapy trials with PARP inhibitors.

Q: *At which point do you regard a patient triple negative in terms of ER and PR levels of negativity? The convention in the US has been to use ASCO/CAP guidelines, which set the threshold very low, so that essentially any ER or PR staining is called positive. We all recognise that this may misclassify some patients. The CALGB triple negative trial allows up to 10%. What has been your experience?*

AD: I think there is no definite answer. We can say that you and I are co-ordinating efforts across the Atlantic, in the context of the BIG and the US intergroup collaborative effort. We are trying to look at some neoadjuvant and adjuvant therapy trials in an attempt to understand if there is a threshold that can tell us when a tumour has to be considered triple negative versus non triple negative. For the time being, my impression is that if a patient is below 10% for ER and PgR, and has HER2-negative status, I would feel comfortable in considering the tumour triple negative, assuming there is ductal infiltrating histology and other characteristics suggesting triple negative status, such as high proliferation.

Q: *Could you comment on the role of bevacizumab in the treatment of triple negative breast cancer? Are there any data?*

AD: Some retrospective analyses have been done in the context of metastatic breast cancer trials where bevacizumab has been tested, but I do not think that these data were strong enough to make any definitive comment on its role in triple negative breast cancer. An ongoing trial is testing bevacizumab in the adjuvant setting after chemotherapy, specifically in triple negative tumours. My impression is there is no strong rationale for thinking that antiangiogenic treatment should be particularly active in triple negative disease.

LC: *I agree. I do not know of any reason to think that bevacizumab works any better or worse in triple negative than in any other subgroup of breast cancer. The forest plot seems to show that the extent to which it works is fairly uniform across all subsets of breast cancer. It is a real challenge for us as to how we select for these drugs as we go forward. The neo-adjuvant CALGB trial also has randomisation to receive or not receive bevacizumab, so that would also be directly tested there in the neoadjuvant setting.*

line treatment of metastatic disease, followed by cyclophosphamide, cisplatin plus iniparib. This study, as well as NeoBIG, has been designed with the aim of obtaining complementary data that can lead to a more rational design of an adjuvant therapy trial in the context of BIG.

- The US NSABP neoadjuvant trial. This is an interesting design proposal, addressing the role of PARP inhibition and the role of anthracyclines, with the primary endpoint of pCR.

The take home message on PARP inhibition is that this is a targeted approach, particularly in tumours carrying DNA repair dysfunction such as triple negative cancers. Several PARP inhibitors (oral and intravenous formulations) are currently being tested in clinical trials. Preliminary data from phase II trials suggest that this new class of agents may be particularly active in triple negative tumours without major safety concerns. Although current data are very provocative, treatment with PARP inhibitors is not yet a 'standard' for daily practice, and no PARP inhibitor has yet been approved. Further results are awaited and these will probably become available in the next year.

Reading the signs

The role of genomic signatures in guiding treatment decisions

Anna Wagstaff

The concept of a genomic signature that can define any tumour according to its unique biology has been central to the emerging paradigm of personalised therapy. But how helpful are multi-gene assays in guiding treatment decisions in clinical practice, and what role can we expect them to play in the future?

Read the signature, choose the treatment. This was the enticing prospect that opened up with the advent of technologies capable of reading the gene expression profile of tens of thousands of genes in tumour tissue.

But more than a decade after these techniques became available, even the two best-known and tested multi-gene assays are not yet part of mainstream clinical practice in Europe. Although Genomic Health's Oncotype DX and Agendia's Mammaprint (both designed to sort high-risk from low-risk breast cancers), show that the technology has got better, quicker and considerably cheaper, the whole field is looking more complex than many had hoped.

It was only two years ago that the St Gallen conference, which has been setting out consensus guidelines for adjuvant treatment of early breast cancer since 1978, first mentioned a role for multi-gene assays, and then only for when traditional clinical and immunohistochemistry tests are inconclusive. As Europe's breast cancer community gathers for the 11th St Gallen conference in March 2011, the role of multi-gene assays in guiding adjuvant treatment will again be up for discussion. Their deliberations will be followed by specialists in other fields – colorectal, lung and prostate cancer – who are also looking for guidance on adjuvant therapy, and wonder how helpful the various multi-gene assays currently being proposed and trialled in their areas could be.

Not so simple

The idea that every tumour could be classified into clinically relevant categories based on the expression of a signature set of genes led to bonanza time for specialist biostatisticians in the 1990s. They found their services in huge demand as competing research groups scrambled to be the first to identify and validate signatory gene sets. But a head-to-head race between teams in Amsterdam and Rotterdam seeking a signature that would differentiate between breast cancers at high risk of recurrence and more indolent tumours gave the first indication things might not be quite so simple. Both signatures proved to be quite effective at predicting prognosis, but only three of the 76 genes used in the Rotterdam signature were also found among the 70 genes making up the Amsterdam signature.

Meanwhile, the general concept of the tumour signature was brought into increasing disrepute as the technology became more widely available and hundreds of disparate studies were conducted in populations where the recurrence rate within the studied population was too low and the numbers of genes being studied – and consequently the number of multiple comparisons – was too high. Commentators

like John Ioannidis from the University of Ioannina in Greece led calls for fewer, larger, better-designed studies, showing that the huge data sets that were being gathered from relatively small numbers of patients were open to almost any interpretation. As he commented at a media 'reality check' in 2007: "with 30,000 genes to choose from, anyone looking for a significant pattern is quite likely to find one," (*Cancer World* Jan/Feb 2008).

His remarks were echoed last year by Rachel Midgley who, as lead clinician in the QUASAR trials, has been examining the evidence for a multi-gene assay to guide treatment in colorectal cancer. She talked about the literature being "replete with rather unconvincing, small studies, which are underpowered, variable in their methodology and quality assurance and which are often linked to incomplete clinical data sets. Even meta-analysis of these sorts of studies is rather suspect … so perhaps it is not surprising that little progress has been made in defining a useful marker, which would help mainstream clinical decision making," (*Cancer Journal* 16:210–213).

Also undermining the concept of a single tumour signature was growing evidence that the biological make up can vary considerably from one region of a tumour to another. One area might test highly positive for amplified HER2 expression, for instance, while another area tests normal. Taken together with the evidence that biology changes over time and in response to treatment, and that the genetic signature of the primary tumour and metastasis can differ greatly, the question arises whether a tumour signature may only apply for a certain place and time. There is also a growing body of evidence that the biology of the non-cancerous host tissue surrounding the tumour plays a major role in determining prognosis and possibly also points to the need for different treatments. Perhaps we need host signatures as well as tumour signatures.

Some specialists also question the value of the information given by the gene signature. Ideally, they argue, targeted therapies should be directed at a functional pathway to which tumour survival is addicted; however, gene status does not reliably correlate with downstream protein status or with pathway function. Thus, the fact that a tumour shows amplified HER2 expression, for instance, does not mean that HER2 is necessarily the driving force, which is why not all patients with HER2-positive tumours benefit from HER2 inhibitors such as transtuzumab (Herceptin). The point is well illustrated by a comparison of the pathways involved in the Amsterdam and Rotterdam gene signatures, which demonstrate that, despite the minimal overlap between the genes, they had 21 pathways in common.

"But it works"

Steve Shak, chief medical officer at Genomic Health, is well-equipped to argue the finer points of targets and functional mechanisms, having come from Genentech, where he led Herceptin through the approval process. But his answer to those who question the usefulness of Oncotype DX is a simple one: it does what it says on the tin – it assists

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

patients and doctors to decide whether to opt for chemotherapy in cases of early ER-positive breast cancers, by indicating the likelihood of recurrence and of response to treatment.

Oncotype DX uses a technique called real-time polymerase chain reaction (RT-PCR) to measure levels of mRNA expression from 21 genes in samples of tumour tissue taken from a standard paraffin bloc. Using these results, it then calculates a 'Recurrence Score' of between 0 and 100, which corresponds to the likelihood of the cancer returning within 10 years. Scores between 0 and 17 are defined as 'low risk'; 18 to 30 as 'intermediate risk' and 31 and above as 'high risk'.

Shak says that the Oncotype DX breast cancer assay has successfully come through the kind of close scrutiny that he and his colleagues welcome. "As a physician or patient I want a test that has demonstrated it really works; that there are multiple studies to show it is fit for the specific purpose for which I am going to be using it," he says. "We worked with leaders in oncology throughout the world to do multiple studies that not only identified the best genes but also validated their use in multiple well-defined rigorous clinical studies. We've now done 14 studies in more than 4000 patients." The use of Oncotype DX to guide adjuvant treatment decisions in early ER-positive breast cancers is now included in the published ASCO clinical guidelines.

Shak readily concedes that the track-record of research into molecular diagnostics in general has not been a glorious one. "When we started Genomic Health in 2000, we looked across a landscape of biomarker research and development, and it was easy at that time to get very depressed. There were tens of thousands of articles on this marker and that marker, and very few if any of those ever made it into clinical practice."

But every new technology comes with its own learning curve, and there are signs now that the field is maturing. In the US, the FDA-led MACQ project is trying to bring some level of quality control to the whole field of microarray, RT-PCR and other 'next-generation sequencing technologies' and promote their proper application in discovery and development. Crucially this includes providing guidelines on the capabilities and limitations of various data analysis methods in developing and validating predictive models, and reaching a consensus on 'best practice'. Mammaprint (which came out of the Amsterdam research) has become the first multi-gene assay to have its prognostic powers recognised by the FDA, although approval by the FDA (or EMA, its European counterpart), is not a requirement for these tests.

Lessons have been learned too about

Multi-gene assays – the story so far

- Gene signatures, or multi-gene assays, can be captured in a variety of ways. Agendia uses the Agilent microarray platform to generate the Mammaprint, which classifies early ER+ breast cancers into high risk and low risk, based on the 70-gene signature originally identified by the Amsterdam team. Alternative microarray platforms include Affymetrix, which was used for the 76-gene Rotterdam assay and has also been used to generate a putative 23-gene signature to predict for recurrence in colon cancer (*JCO* 27:1564 –1571). This technology requires frozen tumour specimens, although new techniques are being developed to enable it to be used with paraffin-embedded specimens as well.
- Genomic Health uses an alternative technology, real-time polymerase chain reaction (RT-PCR), to read the 21-gene signature that forms the basis of the Oncotype DX multi-gene assay for breast cancer. This assay generates a Recurrence Score for each tumour of between 1 and 100. This can be done using paraffin-embedded tissue.
- Agendia argues that Mammaprint is more helpful, in that it rates tumours as either 'high risk' or 'low risk', thus avoiding the chance that readings may come back as inconclusive. Genomic Health counters that all the evidence shows the biology of ER+ breast cancers to be a continuous variable, and that giving risk according to a continuous recurrence score is therefore more accurate.
- There is disagreement also over which of the two assays can claim greater validity. Mammaprint is the only assay whose powers to predict outcome have been approved by the FDA. On the strength of this and other evidence, it is now reimbursed by Medicare in the US. However, Oncotype DX is the only assay to be included in the ASCO clinical guidelines as a tool for deciding who will benefit from chemotherapy (*JCO* 25:5287–5312), and it too is reimbursed by Medicare as well as Medicaid and the major US health insurers. The evidence levels behind the decision to include only Oncotype DX in the guidelines has been a point of debate (*JCO* 25:2057–2058; *JCO* 2058–2059; *JNCI* 101:1456–1452). More information about their relative merits will be available with the results of the large Tailor X and MINDACT trials, but these are not due to report final results for many years yet.

CORBIS/ED KASHI

Do I have to do this? Finding more accurate ways to predict who will benefit from chemotherapy and who will not would save countless cancer patients unnecessary suffering and cut healthcare costs

the need for a more collaborative approach to secure the patient numbers necessary to provide reliable results. Trials the size of MINDACT and TailorX, which seek to establish how effectively Mammaprint and Onctopye DX predict who will benefit from adjuvant chemotherapy, have enrolled many thousands of patients who will be followed for many years. When they were set up, it was hard to envisage studies of a similar scale outside of the highly organised and well-funded field of breast cancer. Yet we are now beginning to see sizeable trials for molecular markers and multi-gene assays being carried out in colorectal cancer by some of the big European and US collaborative groups, including a variant of Oncotype DX for predicting recurrence risk in colon cancer, being tested by the US NSABP (National Surgical Breast and Bowel Project) using tumour tissue from the QUASAR trials (see p 27, Beyond breast cancer).

The scientific rationale

The validity of these multi-gene assays rests on more than just the statistical evidence that they work, says Shak. The set of 21 genes used for the Oncotype DX assay – 16 'cancer genes' and five reference genes – make sense in terms of what is already known about the biology of breast cancer. "We picked the genes because when we looked across the studies they provided evidence that they really work. But the [cancer] genes actually turned out to be in four groups and then three independent genes." Those four groups, he explains, relate to proliferation, oestrogen receptors, HER2 and invasion. "It was very reassuring to us that, when the genes revealed themselves in terms of which ones worked, they actually did group themselves in a way that was very relevant to our understanding of breast cancer biology."

This remains true, argues Shak, even if you look at some of the most recent evidence about the biology of the host tissue. CD 68, a monocyte macrophage-related gene involved in the body's immune system is one of the 21 signature genes. "That gene relates to the host response to the tumour. So our test captures information about the tumour and host response and integrates it to give single score that is relevant for selection of the right treatment."

As for the argument that mRNA measures do not provide the most accurate reflection of the signalling pathways that are driving the tumour, Shak is pragmatic, describing himself as 'agnostic' on whether DNA, RNA or protein offers the most useful information. Genomic Health opted for measuring mRNA using the RT-PCR technique, he says, because with the technology currently available, that is what works best. "Proteins are complicated, they undergo clipping and post-translational modifications, the assays to look at them are complicated and challenging and I think the issue is not one of which is more important, but which one can be practically harnessed to serve patients."

Indeed, the practicality of the Oncotype DX test is widely regarded as one if its big advantages, because it can be done using paraffin-embedded tumour blocs that are routinely collected for pathology reports, it can be delivered by any overnight courier service and Genomic Health prides itself on a high level of quality control and can point to an excellent track record of reproducibility and accuracy.

We are beginning to see sizeable trials for multi-gene assays carried out in colorectal cancer

The issue becomes one of how much additional information the multi-gene assay can supply

View from the clinic

Catherine Oakman, a medical oncologist with a special interest in breast cancer based at the Sandro Pitigliani Medical Oncology Unit, in Prato Hospital, Italy, will be among the many making the journey to St Gallen this March to learn more about how evidence that has emerged since March 2009 might impact on guidelines for clinical practice.

Lead author of an overview piece on breast cancer assessment tools and optimising adjuvant therapy, published at the end of last year in *Nature Reviews Clinical Oncology* (vol 7, pp 725–732), Oakman follows the recommendations of the St Gallen 2009 consensus, which pose the role of multi-gene assays as a last rather than a first step in consideration of adjuvant chemotherapy for a woman with ER-positive disease.

Mammaprint and Oncotype DX can both provide a molecular picture of biological features, says Oakman, but tumours are already assessed by clinical features – tumour size and lymph node involvement – and by histopathological features – morphology, and ER, PgR, HER2 and Ki-67 (proliferation) status. These are all captured by the traditional St Gallen criteria, she says, so the issue becomes one of how much additional information the multi-gene assay can supply.

"St Gallen criteria are very practical because they incorporate tumour parameters which are readily assessed in daily clinical practice. With that information you can make a therapy decision for most patients. For individuals with ER-positive disease in whom you are still unclear about additional benefit of chemotherapy over endocrine therapy alone, the St Gallen consensus advises consideration of a genomic test. The genomic test comes at the end and only if you are unsure."

She does concede that the reliability of immunohistochemical markers has been a problem. In trials where local pathology reports are quality controlled by a central laboratory, discrepancies of up to 20% have been found for ER, PgR and HER2. All the tests involve some level of reader evaluation, and until recently there was no standard agreement about where to set the diagnostic thresholds.

Improvements may come, says Oakman, from close working relationships between oncologists and pathologists, and standardisation of pathology testing – something she believes is already happening in a number of ways.

Greater involvement in multidisciplinary teams means pathologists are increasingly aware of how the results they report are used to guide treatment decisions, and this gives them an enormous incentive to get the most accurate results they can. There are also new step-by-step guidelines, published by ASCO in conjunction with the US College of American Pathologists (CAP), for testing ER, PgR and HER2. They can be implemented in any hospital laboratory, and though they are not binding, they set a quality standard by which any hospital can be evaluated.

ASCO-CAP guidelines have now set the threshold for ER and PgR positivity as at least 1% of tumour nuclei staining positive. The Ki-67 proliferation marker, however, remains problematic both in terms of an agreed threshold and standards for testing. Oakman accepts that genomic markers are currently superior in robustly and reproducibly measuring proliferation, but argues that given time, standards and guidelines may bring more reliability to this marker as well.

For some patients, treatment decisions are fairly clear. Evidence shows that, in general, tumours with a very high ER and PgR status are sensitive to endocrine therapy but derive little additional benefit from chemotherapy. Individuals with HER2-positive tumours are likely to derive benefit from trastuzumab, and this is always given alongside chemotherapy. For triple negative disease, chemotherapy is the only currently available systemic option.

The problem arises where tumours stain positive for ER, but show some signs of a more aggressive cancer, for instance low PgR, grade 2, intermediate Ki-67 and/or some nodal involvement. This represents a sizable group of women, as about one third of the 75% of patients with an ER+ tumour fall into this uncertain category, and the question of whether these patients might derive additional benefit from chemotherapy over endocrine therapy alone is unclear. "This is the group of patients where genomic tests might help," says Oakman, "That is of course if, firstly, the patient can afford or has insurance to cover the substantial cost, and secondly, if she would be agreeable to chemotherapy if the results showed her genomic risk to be high."

Even then, there is no guarantee that the genomic test will provide the guidance doctor and patient are looking for. "If such a patient is assessed as high or low risk by Oncotype DX, this helps treatment decisions. However if such a patient is assessed as intermediate risk, I am still

unclear about the estimated additional chemotherapy benefit," says Oakman. Shak, from Genomic Health, cites a survey indicating that in 30% of cases, testing with Oncotype DX does in fact lead to a change in the initial decision on treatment. This is not something Oakman is able to confirm from her own experience.

Currently both Oncotype DX and Mammaprint are reimbursed in some European states, but so far only by a small minority of social insurance providers. Oakman suggests it would be best to wait for the results of the TailorX and MINDACT trials to get a clear picture of their powers to predict benefit from chemotherapy in this patient subgroup, before deciding whether public health insurances should cover the cost of genomic tests, at least when traditional markers are inconclusive.

Are genomic tests the future?

Tailoring treatments to patients is a strategic goal for oncology. For many people, this paradigm is all about tracking down targets and designing biological therapies that can block them, and this remains the great hope for the future.

For the moment, however, chemotherapy remains a mainstay of treatment for many cancers, and as early detection strategies ensure more and more cancers are caught at an early stage, the ability to sort the patients who will derive benefit from these toxic treatments from those who will not is by far the greatest 'personalisation' issue in terms of the numbers of patients affected.

Using current regimens in stage II colorectal cancer, for instance, curing an additional three to four patients requires putting one hundred patients through chemotherapy, 40% of whom will suffer significant toxicity. The future for genomic tests like Oncotype DX and Mammaprint will lie in how far they outperform traditional clinical and pathological criteria and how the costs stack up against the benefits for patients and the savings for health services.

However, even if the trials show beyond doubt that these genomic tests have clinical value, they still predict only 'general chemosensitivity' rather than specifying a treatment. The quest for predictive biomarkers for specific chemotherapies is another level of sophistication for the future (see also Treatment of Triple Negative Breast Cancer, p 13).

Beyond breast cancer

In January last year Genomic Health launched an Oncotype DX (RT-PCR) assay for predicting the risk of recurrence in patients with stage II colon cancer (defined as involvement of the bowel wall without lymph-node involvement). The 12-gene assay was shown to be significantly predictive in sorting those with a 'low' risk of recurrence (8%–10% within three years) from those with a 'high' risk (20%–25% risk (*JCO* 27 (15s): abstract 4000).

This January, results from a trial of Agendia's experimental 18-gene Coloprint microarray assay were published (*JCO* 29:17–24), showing it too was significantly predictive at sorting stage II and III patients at 'low' risk of recurrence (around 12.5% recurrence at five years) from those at 'high' risk (around 33% at five years).

Neither study claimed to provide statistical proof that the assays could predict who would benefit from chemotherapy. However, David Kerr, one of the leaders of the QUASAR trial that collaborated in the study of the Oncotype DX assay, said, "When you look at the totality of the data, we think that the new assay provides a clinically useful tool for [identifying] which stage II colon cancer patients should be selected for chemotherapy," (*Medscape* 19 May 2010).

Roberto Labianca, lead author of ESMO's clinical guidelines for diagnosis, adjuvant treatment and follow-up of primary colon cancer (*Ann Oncol* 21 Supp 5: v70–v77), insists, however, that while these data are interesting in the context of the wider search for biological markers that can predict response to treatment in this patient group, they are not sufficiently robust to merit being included in guidelines for adjuvant treatment. For the moment, he says, decisions on adjuvant treatment should continue to be guided by clinical and pathological markers which define stage II disease as high risk according to involvement of the bowel wall, invasion of vascular, neural or lymphatic vessels inside the tumour tissue, obstruction or perforation of the tumour during surgery, or where fewer than 12 nodes have been examined.

The search is also on for multi-gene assays that might predict recurrence and benefit from treatment in many other cancers. Tests for prostate cancer and non-small-cell lung cancer both feature in the Genomic Health pipeline.

Genomic tests are reimbursed in some European states, but only by a small minority of social health insurers

Think before you ruin your patient's chance of parenthood

Prize for journalist who highlighted poor practice in Poland

The plight of cancer patients for whom treatment means risking losing the opportunity to have children was taken up in Poland by the leading national daily *Gazeta Wyborcza*, in a piece that earned reporter **Sławomir Zagórski** a Best Cancer Reporter Award. The article, titled "I had cancer, I'm going to be a Dad," is reprinted below.

In Poland, being cured of cancer can often mean being sentenced to infertility. The price paid for intensive cancer therapy hits young people just starting out in life especially hard. But it doesn't have to be that way.

"These days, patients treated for cancer can in most cases conceive and give birth to healthy children," insists Professor Mariusz Bidziński, Chairman of the Polish Association for Oncological Gynaecology and Head of the Gynaecological Cancer Clinic at the Warsaw Cancer Centre, "There is, however, one condition – action needs to be taken before, rather than after, starting cancer treatment," explains the specialist.

But in Poland few people give it any thought. Patients are terrified by the diagnosis, and their main concern is to save themselves. According to Bidziński, they are rarely told that treatment can result in infertility. Doctors tend to focus on treating patients, rather than worrying about what might happen to them a few years down the line.

"Not a single one of my colleagues at the Warsaw Cancer Centre has ever come to seek my opinion on this matter," says Bidziński. "Some of them are treating young women who, after therapy, can forget about becoming mothers," he adds.

"In Germany, France, the Benelux countries or the USA, a discussion is held with the patient about whether, after successful cancer treatment, he or she is going to want to have children – this is standard procedure," says Dr Kamil Zalewski, who works at Bidziński's clinic. "Not only that, but if a doctor in one of our western neighbours should forget to raise the subject in talks with the patient, he or she may well have to answer for it before the courts," Zalewski points out. "And here in Poland? Forget it!"

Maybe Polish specialists would be willing to refer at least younger patients for consultation, but where to? In our country we don't have a single centre where a frightened young man or woman can seek comprehensive help, where they can talk about becoming a parent, not just with a cancer specialist but also, for example, with a specialist in infertility treatment or a psychologist. A few well-informed – and well-off – patients seek help of their own accord from private *in-vitro* fertilisation clinics.

Sławomir Zagórski

gazeta WYBORCZA.PL

Many techniques are available to enable cancer patients to keep open the option of having children even if the treatment renders them infertile. This article looks at what must change in Poland to ensure patients get the chance to make use of these techniques in time


Miałem raka, będę tatą

Nauka

120 tys.

6 tys.

A WORD ABOUT BONE-MARROW TRANSPLANTS

Diseases whose treatments lead particularly frequently to infertility in both sexes include cancers requiring bone-marrow transplantation (certain forms of leukaemia or lymphomas, e.g. Hodgkin's disease) and also some sarcomas. The chances that a twenty-year-old woman, after undergoing cancer treatment, will get pregnant spontaneously (i.e., without medical help) are as a rule no more than five per cent. "The cancer itself doesn't have to affect the reproductive system – the ovaries or uterus," explains Zalewski. "Aggressive chemotherapy, in cases of breast cancer for example, is frequently all it takes for the ovaries to stop working. And when they do stop working, it not only means the end of all dreams of motherhood, it also means a fall in oestrogen production and early onset of the menopause," he adds.

Men are not spared either. If, for example, a twenty-year-old man has to have a bone-marrow transplant, doctors must first completely destroy his own diseased bone marrow, using drugs or radiation. In four cases out of five, such pre-transplant radiation conditioning fatally damages the delicate Leydig cells in the patient's testicles. If the patient does manage to survive the cancer, in 80% of cases his semen will never again contain even a single sperm cell.

In patients with testicular cancer (a disease that affects mainly young men) chemotherapy and specialist surgical procedures on abdominal lymph nodes can reduce the ability to procreate.

PREGNANCY FROM THE FREEZER

What can be done, given that the cancer has to be treated?

The first thing to do is talk to the patient. Ask whether, after successful treatment, he or she is planning – even if only tentatively – to have children. "At least half the young people [up to the age of 35] in Poland who suffer from cancer– i.e. 3000 a year – will answer such a question affirmatively," says Bidziński.

If a patient expresses the wish to become a parent, then action needs to be taken – and without delay, because cancer doesn't wait.

In the case of men, the situation is relatively straightforward. All that is required is an andrological examination to check that the semen contains sperm cells, after which the semen is frozen. This can be safely stored in liquid nitrogen for years.

With women, it is more difficult, but in this area medicine is constantly coming up with new methods of dealing with the situation. One method relies on

"Ask whether, after successful treatment, he or she is planning – even if only tentatively – to have children"

freezing egg cells, though unfortunately this is still meeting with considerable resistance (barely a few hundred successful pregnancies have been achieved this way across the world). Incomparably simpler is the business of freezing ready embryos, but obtaining such an embryo also requires a sperm cell. If a young woman already has a husband or partner, the couple can decide to have embryos prepared and freeze them. If she doesn't have a partner, she can elect to be fertilised by sperm from an anonymous donor, though such a solution is, of course, not for everyone.

For some years now, doctors have been (successfully) testing a new method of preserving fertility in women undergoing chemo- or radiotherapy. Before the treatment, the surgeon cuts out one of the ovaries (or a fragment of one) through a small incision in the abdomen, and removes tissue from it, which is cut into thin strips and then frozen. After the anti-cancer treatment is completed, and once it is certain that the patient has completely recovered from the disease, the tissue can be thawed, checked to confirm that there are no cancer cells present, and grafted onto the remaining ovary. It transpires that the thawed tissue gets to work and is soon able to produce normal egg cells.

This technique was pioneered by Professor Jacques Donnez of the Catholic University in Louvain (Belgium). An article six years ago in *The Lancet* brought news of the first baby to be born in his clinic following freezing and transplantation of fragments of ovary. Jacques Donnez's patient had been suffering from Hodgkin's disease. Four months after grafting the fragments of preserved ovary, the patient's periods returned, and a few months later she went into labour perfectly naturally, without having to resort to *in-vitro* techniques.

Since 2004 many more babies have come into the world from frozen and thawed ovary tissue – in Poland, no-one has tried it yet.

What about the youngest patients?

Freezing ovarian tissue should in future offer hope of motherhood even for young girls who have yet to enter puberty (children get cancer too – in Poland there are about 1200 new patients a year). Doctors are hoping that immature egg cells recovered from such tissue will one day serve for *in-vitro* fertilisation.

Specialists are also looking at ways to help boys who are not yet producing sperm cells. Researchers in Israel are freezing testicular tissue fragments collected from very young cancer patients. It is not yet known whether this technique will work, but trials are continuing.

One thing that can be done without difficulty, even now is the fairly simple procedure of moving women's ovaries away from irradiated areas – in cases of cervical cancer, among others (such procedures are being performed in Poland; no need here for any major operation, as access to the ovaries can be obtained through two small openings in the abdomen).

Doctors are also experimenting with removing only the cancerous tissue rather than the entire uterus where the cancer is caught early, again with a view to preserving patients' future ability to parent children. Such conservative procedures have made possible the birth of almost 500 babies around the world (two of them in Poland).

Cancer and in-vitro techniques

One of Bidziński's dreams is the creation of a centre in Poland that would be responsible for the complex care of young cancer patients wanting to become parents in the future. "All it would take would be a measure of good will on the part of the authorities, a bit of equipment and some funding," the specialist argues. "Patients would be treated for cancer where they live, and they would come here purely for consultation and possibly to have their semen, egg cells or fragments of ovary collected."

The question arises, however, as to who is going to pay for such services and for the cost of storing patients' tissues. "Despite the fact that we have been trying for years to persuade patients to make use of sperm banks, very few do," maintains Dr Iwona Skoneczna of the Warsaw Cancer Centre.

At present, Poland is still not providing any kind of help to its infertile citizens. Yet, as if not enough money were already being spent on cancer treatment, cancer patients can still demand help for later infertility treatment.

"Paradoxically, it could be cancer patients who are eventually the first to benefit from such help," Bidziński speculates. "After all, hasn't fate already given them a raw deal? Perhaps we who are healthy and happy in our lives could devote a little of our money and energy to helping them out."

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A simple doctor's quest to improve on today's treatments

How Stan Kaye came to lead drug development at the Royal Marsden

➜ Simon Crompton

Treating patients who are urgently searching for new therapies is tough and doesn't get any easier, says **Stan Kaye**, head of drug development at the Royal Marsden. He treasures the moments when a new drug turns up that shows real value. The big challenge for medical oncology is to understand who benefits from what; success depends on attracting to the field the brightest and the best.

By his own assessment, he is a "simple doctor", not a scientist. Stan Kaye works in an office of few pretensions, displaying pictures of past players from his beloved Leeds United Football Club rather than professional accolades. He is quiet but avuncular, and says he was never particularly ambitious. Yet it was a simple doctor's motivation – to end the suffering brought on patients by frankly inadequate cancer treatments – that brought him to lead one of the most important early clinical trials units in Europe.

As head of the Drug Development Unit at the Royal Marsden Hospital in Sutton, England, and the chairman of the Institute of Cancer Research's Section of Medicine, Kaye is now overseeing the first use in humans of a range of new targeted therapies that could transform cancer treatment in the next decade.

He finds it hard to conceal his excitement, for instance, about the potential of PARP inhibitors – a class of drug whose possibilities were first recognised by scientists at the Institute of Cancer Research six years ago, and were subject to their first extended single-agent clinical trials at the Royal Marsden three years ago. The drugs have yet to reach the market, but there is accumulating evidence that they will bring significant benefits to many patients with breast and ovarian cancer, and possibly others including prostate, endometrial and colon cancer.

"We are genuinely moving from chemotherapy to much smarter treatments based on a better understanding of what causes cancer, and what distinguishes cancer cells from normal cells," he says. "This knowledge is being turned into new treatments, often given as tablets, that make people's tumours shrink, and it's just terrific. So in the next few years there's going to be an increasing understanding that you don't treat all people with a particular type of cancer in the same way, and indi-

INSTITUTE OF CANCER RESEARCH

vidualised treatment will increasingly take over."

It's all a far cry from his early days as a researcher in the 1980s, when he was driven by seeing how "lousy" current treatments were. The past five years is bringing something truly different, and he can afford to be optimistic.

Kaye's excitement about PARP inhibitors is related to his own special interest, ovarian cancer, where the drug is showing particular promise in helping both common types and rarer familial forms linked to BRCA mutation. During phase I trials at the Drug Development Unit, Kaye and his team on the clinical side worked closely with scientists who had developed the drug. In the first trial, 19 patients with advanced ovarian, breast and prostate cancer, who were all BRCA gene mutation carriers, were given the new medication, having exhausted other forms of treatment.

"Early on, even in the first patients treated, we knew we were on to something. It only happens rarely that you see a new treatment really making a difference at this early stage. We couldn't believe the first data because, in half the patients, the tumours shrank. The drug had very modest toxicity and patients said, 'This is nothing like chemotherapy.' So we were delighted when an international trial showed the same thing – roughly 50% response rate in recurrent ovarian cancer." The drug could constitute a significant leap forward for ovarian cancer, Kaye reflects, where developments have been slow in recent decades and largely focused on improved multidisciplinary care rather than good drugs.

The Drug Development Unit at the Royal Marsden, one of the biggest in the world, is buried in the hospital's sprawling site in Sutton – Lego-style blocks, puddle-strewn car parks, a muddy building site and the faded Victorian monument where Kaye has his office. Around 600 patients with cancer that

WHO BENEFITS FROM PARP INHIBITORS?

Mutation of BRCA1 and BRCA2 genes has been linked to hereditary breast, ovarian and prostate cancer. In 2005, the Institute of Cancer Research team in Chelsea, led by Alan Ashworth, discovered that, because these genes were not functioning, DNA repair was defective, and these cancers were therefore exquisitely sensitive to drugs blocking an enzyme called PARP. Early trials of these PARP-inhibitors at the Drug Development Unit showed that around 50% of tumours shrank. This result was replicated in an international trial. Last year, it was announced that Ashworth's team had discovered that the drug would also kill cancer cells with other types of gene faults apart from BRCA inherited cancers, so its potential is much broader than originally thought. The drug is now moving into phase III trials. According to Kaye, the beauty of PARP inhibitors is that doctors should be able to predict exactly who will benefit from them, because the genetic defect that makes people responsive will have a biomarker.

has progressed despite conventional treatment come here every year to enter phase I trials of experimental cancer drugs, knowing that the odds are that the drug won't help, but that there is a chance that others will benefit from the knowledge gained, even if they do not. The centre takes the genetic discoveries made at the Institute of Cancer Research's facilities in Chelsea, London, converts them into drugs, and offers them to patients with advanced cancer. Funding comes partly from the drug companies that are jointly developing the drugs, as well as from Cancer Research UK and the Department of Health.

TRANSLATING GOOD SCIENCE INTO GOOD TREATMENTS

In the 10 years that Kaye has been in charge of the centre, he's closed the gap between the hospital and the Institute of Cancer Research, distilling a disparate phase I operation scattered across the hospital into a single specialist ward with 25 nurses, 15 doctors and 80 staff all working exclusively on the trials. These changes involved major restructuring at the Royal Marsden Hospital site at Sutton.

It produced a centre that is leading the way, not only in drug development, but in the way that early trials are performed. Phase I trials, believes Kaye, are about to become more important than they have ever been, and the Royal Marsden's dedication to speeding up the translation of good science into good treatments is showing the way ahead.

Towards better treatments. Catching up with fellow specialists at the 4th Ovarian Consensus Conference in Germany, 2004

"The nature of phase I trials has changed a lot since we conducted our first one in the mid-1980s in Glasgow. For instance, I did a trial with a drug company of a green compound. It had some striking effects in the experimental model, and it seemed safe enough, but it went into the clinic without me having any idea of how it worked. This is something we would rarely do now. We need to know if a drug is hitting its target, and the way they are assessed involves sophisticated biomarker work. You just wouldn't do trials now without all that, but in the old days we did."

"It will continue to get better if we get smarter at finding out which patients should get these targeted drugs"

"Oncology requires no specialist manual skills, so it stands or falls on the quality of people who come into it"

The result is likely to be safer treatments and a more rational basis on which to decide whether or not a drug might go forward. The majority of drugs fail – less than 10% of the drugs that go into phase I trials succeed. "But its getting better," says Kaye. "It will only continue to get better if we get smarter at this whole business of understanding which are the patients who should get these targeted drugs."

Nowadays, phase I studies are far more than the experiments in safety they used to be. "They aim to establish correct dosages, indicate substantial activity, and to expand the number of patients involved with a real expectation of benefit."

Kaye continually emphasises that patients need to be realistic about the prospect of significant improvements in phase I trials. But the chance of benefit is still there; for instance, in a study published in 2010, potential clinical benefit was seen in up to 20% of women with metastatic breast cancer taking part in trials of novel approaches at the Marsden between 2002 and 2009 (*Br J Cancer* 103:607–612).

Though phase I trials for cancer drugs inevitably involve only those with advanced cancer who have exhausted all other options, the findings from these trials often have implications for treating cancer at much earlier stages. So for individual patients, and the greater cause of developing better cancer drugs quicker, Kaye believes that an expansion of phase I studies – not just at the Marsden but nationally and internationally – is the way forward.

"First-in-man studies are very demanding. You are having to give small numbers of patients escalating doses, and work out over the course of six months or so what might be an appropriate dose and what the ups and downs of that drug could be. Having got to that point, you need to understand whether that drug is going to be successful – and you may well want to treat a number of patients with a particular tumour type or particular molecular characteristics to understand more. For that kind of work, where you've gone beyond the first-in-man part, we need more facilities. Cancer Research UK is setting up networks across the UK to help with that process."

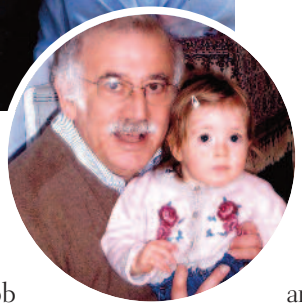
"So the distinction between phase I and phase II studies is blurring to such an extent that conventional phase II studies may not in some cases be appropriate. Having established a significant level of activity in an expanded phase I study, the next step might be a randomised phase II study." The days of single-arm non-randomised phase II trials may be numbered, he says.

An accidental oncologist

Kaye is what you might call an accidental oncologist. Born and bred in Leeds, his father was a Polish leatherworker (his name was originally Krakowski) who came to Britain with the Polish army during the last war.

Kaye ended up going to medical school because he was good at biology and chemistry at school, and his parents wanted him to follow a profession. Those he studied with at Charing Cross Hospital have

Vital support. Meg Morrison, of the UK Cancer Research Campaign (forerunner of CRUK) presents a cheque, dated June 1988, to support the research work being carried out by Kaye and his colleagues at the University of Glasgow



Three generations. With his wife Anna at their daughter Sarah's wedding, and (right) with his first grandchild Hollie, December 2010

remained lifelong friends. One, Bob Leonard, a football and squash pal, had started a job in oncology at Charing Cross Hospital and urged Kaye to join him, a year after qualification. Kaye knew little of oncology, but was looking for an interesting hospital job at that time.

He came under the supervision of Ken Bagshawe, one of the founding fathers of medical oncology in the UK, and was bowled over by the lifesaving potential of chemotherapy for young women with gestational trophoblastic tumours, who came from all over the country to be treated by Bagshawe and his team. "Their recovery was remarkable, and I thought: this is great. I knew I wanted to be an oncologist."

The experience has been influential throughout his career. Oncology, he points out, is a new specialty, which has changed immensely over its 40 years. Unlike specialties like surgery, oncology requires no specialist manual skills. "That means it stands or falls on the quality of people who come into it," says Kaye. He believes that inspiring others to follow is part and parcel of what oncologists should do, and like Bagshawe he has tried to open other doctors' eyes to the potential of the specialty.

He was able to do this during 20 happy years in Glasgow, where he took up the post of senior lecturer at the University's Department of Clinical Oncology in 1981, becoming professor and head of the Medical Oncology Department in 1985. It was a small unit, which grew substantially over 15 years, and Kaye was busy covering a wide range of clinical areas. The students and doctors he taught there have become part of a "Glasgow mafia" that he has maintained contact with. One is Johann de Bono, who joined Kaye at the Institute of Cancer Research eight years ago, and uncovered the exciting potential of the new hormonal therapy abiraterone to treat cases of advanced prostate cancer.

"There are people here who may prove to be more successful than me. One of the things I enjoy most is encouraging and watching young folk who are involved in this area, and because of the reputation of the Drug Development Unit, we get super doctors from all over the world."

Kaye's clubbability has served him and those he has inspired well, and it's a matter of satisfaction to him to see what such informal networks achieved. He became involved in the European Organisation for Research and Treatment of Cancer in 1980, chairing the Early Clinical Trials Group and the Scientific Audit Committee. "Drug development then was a completely different world. We worked in a small group of just 12 or so European colleagues," says Kaye. Drug companies didn't seem so committed to drug development in cancer. "What's changed is there's been so much expansion, so much to work with, so much to learn, that we've lost the concept of a relatively small group of people working together, and EORTC doesn't need an Early Clinical Trials Group because all the major centres are doing their own thing." While that is a welcome development in some ways, Kaye emphasises that maintaining links across Europe between like-minded clinical researchers remains essential.

Driven by the tough end of cancer

Kaye's stories of drug development often incorporate tales of patients' faces lighting up, or their generous comments. His relationship with them – whether it be inspiring or problematic – has always been foremost in his motivations. "My research was always from the point of view of someone whose main job was seeing patients with cancer. If I have any kind of mission, it's that I've been seeing the tough end

ROYAL MARSDEN HOSPITAL

Meet the team. All phase I trials at the Royal Marsden are carried out in a single specialist ward by this dedicated team of medical, nursing and support staff and research fellows

of cancer treatment for a long time, and I don't like it really. It's tough. It doesn't get easier looking after young patients who are desperately looking for new treatments because their disease is going to be fatal. I think that links together with my sense of what the new science offers, to drive me."

He's now 62 and revelling in the recent birth of his first granddaughter. His wife and eldest son are both GPs, and he has two other grown up children who have flown the nest (one a teacher and one an embryo film maker). Though he admits to wanting – one day – to see a bit more of the world than he manages to glimpse from airports and international conference centres, he's not banking on retiring just yet. There are too many plans to put in place.

Out of those muddy puddles between the Royal Marsden buildings is about to spring a new Centre for Molecular Pathology – a research centre, funded through Department of Health research support, that will speed up the process of introducing personalised medicine in daily patient care. It links with Cancer Research UK's initiative to introduce "stratified medicine", where patients with cancer have their tissue sampled with state of the art molecular techniques, to diagnose and target treatment. This is already part of what the Drug Development Unit does, but now, with the new Centre, there's the potential to make their pioneering techniques more widely available to cancer patients. And ending "lousy" cancer treatments for good.

"What's most exciting now is the potential for targeted treatment on a routine basis – patients having their tumour DNA sequence recorded regularly," says Kaye. "It needs expensive equipment, and the Centre for Molecular Pathology will help us with that hardware. I'm hoping that, over the next few years, that will become a standard procedure here, and if we can show the way, I think it's feasible that it will become available nationally."

"One of the things I enjoy most is encouraging and watching young folk who are involved in this area"

Where are the consensus guidelines for women with metastatic disease?

New conference will tackle this neglected topic head on

Marc Beishon

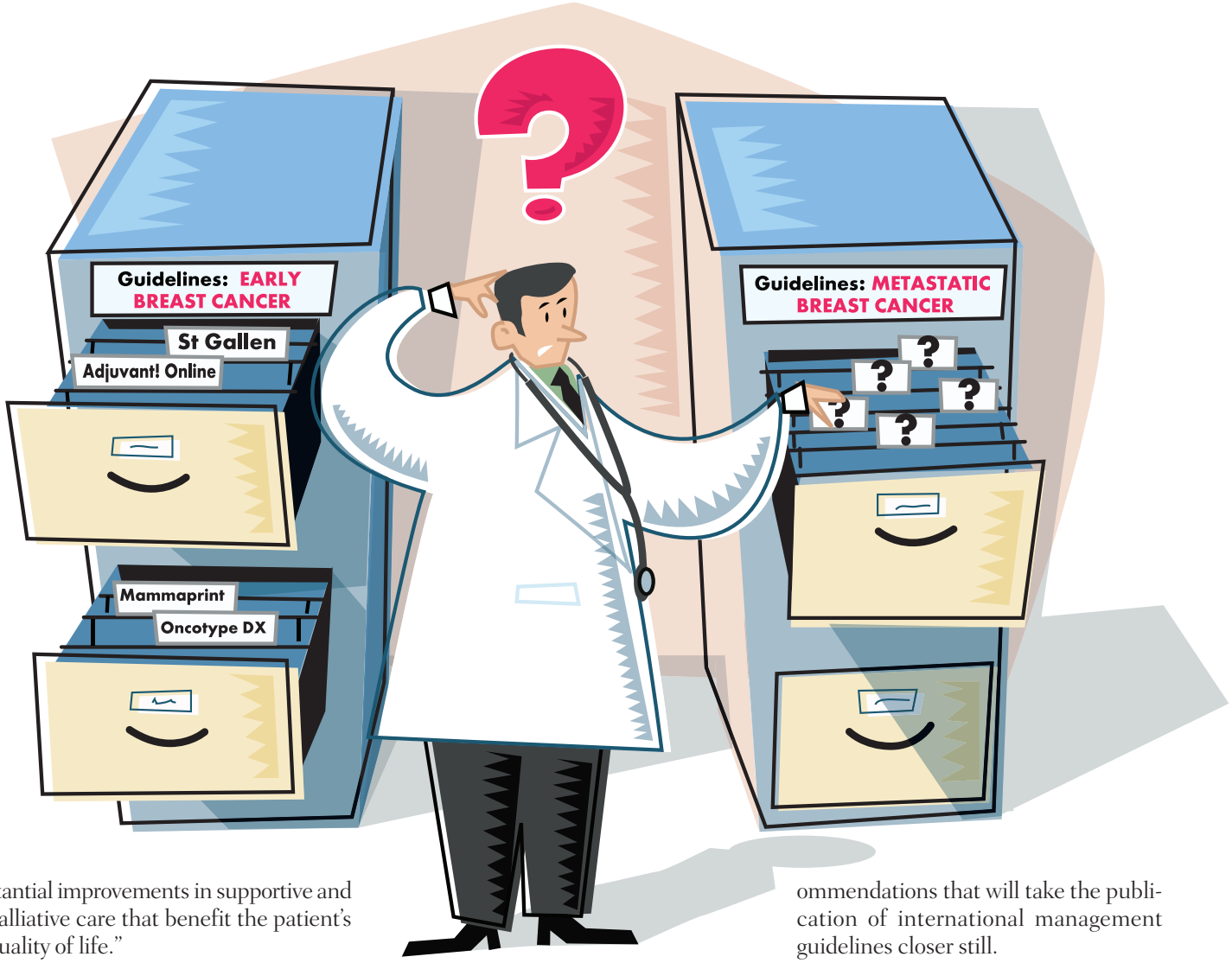
Women with advanced breast cancer can live a full and active life. But median survival is still hovering around three years and the pace of progress is frustratingly slow. A new conference now seeks to develop a more evidence-based approach for treating and caring for women with metastatic disease, so they can benefit from the progress in knowledge and technology that has done so much to improve outcomes in early breast cancer.

This year, a new, regular conference will convene that will challenge a long-standing and often forgotten issue in oncology – that there is little we can do to greatly improve the outcome for advanced breast cancer. Despite the plethora of meetings, research and experts already focusing on breast cancer, metastatic disease has been neglected for treatment and management guidelines in favour of the early stages because of its difficulty and complexity.

That is simply not good enough, say the clinicians behind the First Advanced Breast Cancer International Consensus Conference (ABC1), to be held in Lisbon this November. Not only are there many questions unanswered about how to manage advanced disease, they say, but also the many women faced with metastatic illness deserve a much more positive, evidence-based approach, and support systems that lessen the all too frequent isolation felt by people with an incurable condition.

"It is metastatic disease that kills patients so we will never cure breast cancer unless we focus much more on its advanced stage," says Fatima Cardoso, who will co-chair and host the conference as head of the breast cancer unit at the new Champalimaud Cancer Center in Lisbon. "Already a small subset of those with metastatic cancer show promise for a cure if we identify and manage them correctly," she adds. "For the majority of patients, however, the aim is to improve length and, especially, quality of life. If we could transform it into a chronic condition it would be a major step forward. But we cannot just give up on aiming for a wider cure – and to do that we have to convince investigators and the industry that it is worthwhile to invest in high quality clinical and translational research that could lead to major gains, as we have done in early-stage disease."

She points out that results from work in early-stage breast cancer are seen as meaningful when they translate into years or even decades of survival, but in the metastatic setting gains are mostly weeks or months at best. "The median survival of advanced disease has improved from two to three years in a decade, and that is not acceptable in my view. But we have made far more sub-



stantial improvements in supportive and palliative care that benefit the patient's quality of life."

The concept behind this new addition to the cancer conference calendar arose from a taskforce on metastatic breast cancer set up in 2006 by ESO and the European Breast Cancer Conference (EBCC). In 2007 the taskforce published a set of recommendation statements in *The Breast* (vol 16, pp 9–10) on managing metastatic breast cancer, with a view to developing detailed guidelines and supporting papers in the following years, with consensus sessions at every EBCC. "At the session on advanced disease at the 2010 EBCC we had 1000 people who came on the last day of the meeting – but a few hours every two years when we bring people together is just not enough for what we need to do," says Cardoso.

Now the aim is for a panel at the new conference to develop consensus recommendations that will take the publication of international management guidelines closer still.

As Cardoso explains, the idea is to establish a conference similar to the St Gallen meeting held every two years in Switzerland, which publishes a consensus paper on early-stage breast cancer treatment. "Studies show that countries that have applied the guidelines developed at St Gallen have improved their survival, and that's what we want for advanced disease too."

But she recognises that it will be a

"Survival in advanced disease has improved from two to three years in a decade, and that is not acceptable"

challenge. "There are of course already a few national and regional guidelines for metastatic disease, but they are not well followed and too many oncologists have given up on the idea that they can help." And there are limitations to existing guidelines, such as a lack of depth on specific needs of advanced breast cancer patients in the light of recent knowledge, she adds. These limitations must be addressed, and doing so at an international level will greatly improve the chances of the 'sceptics' in the cancer community taking guidelines seriously, Cardoso feels.

The sceptics' case is mainly that there are too many variables in advanced breast cancer patients for guidelines to be worthwhile, particularly after the usual first-line treatments have been applied. Then it becomes more 'art' than science. Cardoso disagrees. "It is not different from early stage disease, where in any case you need to adapt guidelines to the patient in front of you by, for example, balancing the side-effects according to the chances of a cure.

"In metastatic disease you have to add quality of life factors and possibly prolongation of life, but not a cure in the majority of cases, so the balance is different and more difficult. But if we are talking about increasingly personalised treatment in the early stages, more than ever now we must also apply the same approach in the metastatic setting."

A marker for personalised management in metastatic disease is the initial set of 12 statements published in *The Breast* (vol 16, pp 9–10), which includes not only brief notes on treatment options applicable then but also the need for psychosocial support, informed decision

A life worth living. The needs of women living with advanced breast cancer – for a longer life and a better quality of life – have tended to be overshadowed by the heavy focus on early disease

making, quality of life assessments and enrolment in well-designed trials. Not surprisingly, given the complexity, a multi/interdisciplinary team is crucial (and this is the first recommendation).

All these areas, and others, need more research, says Cardoso. The many questions about drugs, in particular, stem from another major obstacle to progress. As she comments, "In drug development, industry and the cooperative research groups tend to see the metastatic research setting only as a bridge to reach the adjuvant stage. This often leaves important management questions for metastatic breast cancer patients unanswered."

It means that even after many years oncologists still have doubts on whether to use certain drugs in sequence or in combination, how many lines to consider, whether maintenance therapy is an option, and so on. With trials linked mainly to a particular single use of a drug, there are huge problems getting funding to do more complex trials, she adds. "I can understand that companies are not interested in supporting this work, but it's harder to accept that even the cooperative groups, which should focus on academic research, are unwilling to do the trials."

The ESO taskforce has, however, now published several review papers on the available data, for example on combination versus sequential single-agent chemotherapy, and on a patient subset who potentially have a chance of a cure because they have only one or a few metastatic lesions, usually on one organ.

But as Cardoso adds, these papers also serve to identify much more research that needs to done, such as quality of life and predictive factors when using chemotherapy regimens, and in the 'curative' paper, crucial questions such as whether to remove a primary tumour in a patient with metastatic disease. A study addressing the latter issue is currently underway in the US with academic funding, and was initially set up as a cooperative study between US and the rest of the world (under the Breast International Group). "But it has been impossible so far to obtain the funds – and perhaps also the willingness – to run this purely academic trial outside the US," she says.

"Another reason we need better

"Countries using St Gallen guidelines have improved survival – that's what we want for advanced disease too"

"We can now offer procedures we couldn't do before, such as stereotactic radiotherapy on brain metastases"

guidelines is that we can now offer procedures we couldn't do before, such as stereotactic radiotherapy on brain metastases," adds Cardoso. "Technology like this is changing how we can manage these patients."

Along with a lack of interest by industry and some clinicians, Cardoso notes that until a few years ago the patient advocacy groups were not the force they could have been for advanced disease. As she writes in an editorial in *The Breast* (vol 18, pp 271–271), patient groups have focused mainly on the prevention, diagnosis and treatment of early breast cancer, which is "totally understandable" given the larger number of women involved and the difficulty of confronting the invariably fatal side of the disease in the advanced stage. But this has left many women with metastatic disease isolated as "forgotten heroes", as she puts it.

Several initiatives are helping to change this. Stella Kyriakides from Cyprus Europa Donna has been on the ESO taskforce from the start, while an international group for metastatic breast cancer has been set up, the MBC Advocacy Working Group, which has published its own consensus report ('Bridging gaps, expanding outreach' – *The Breast* 18:273–275). This brief report identifies three priorities: improving access to information, resources and support services; raising the profile of metastatic disease within the wider breast cancer community and with the public; and increasing understanding of and access to clinical trials.

A lack of participation in trials was highlighted by an project allied to the MBC Advocacy Working Group, the Bridge survey of 950 women in nine countries with metastatic disease.

In Lisbon, national advocacy groups such as the Breast Cancer Network Australia and AdvancedBC.org in the US will be highlighting work they are doing to support those living with metastatic breast cancer. AdvancedBC.org is run by Musa Mayer, an advocate who has written extensively on breast cancer and has been a pioneer in raising awareness of advanced disease. In a paper published last year (*Seminars in Oncology Nursing* 26:195–202), she examines key lessons learned from surveys of need, such as the Bridge survey. "Patients and families want, need and deserve better services," she says.

See you in Lisbon. Up until now, discussions about treatment of advanced breast cancer have had to be slotted into a single session at broader conferences

In the lead up to the November consensus meeting, Cardoso says more work is being done on themes such as whether it is helpful to detect metastatic disease before it becomes symptomatic, and how to follow up and treat patients, given that tests can be demanding and time consuming. "We are also looking more at the role of maintenance therapy, the number of treatment lines to give and we would like to do much more on psychosocial support for patients and their families."

As she concludes, the pioneers in early-stage breast cancer had their sceptics too. "Just look at Gianni Bonadonna's work on adjuvant chemotherapy in the 1970s – half the scientific world did not believe it would work," she says. "Our work now may seem very difficult but it doesn't scare me."

- A webcast of the workshop on metastatic breast cancer guidelines at the 2010 EBCC is at tinyurl.com/32txp8c (on the ECCO website).
- Both the MBC Advocacy Working Group and the Bridge survey are supported by Pfizer Oncology. See www.bridgembc.com for the consensus report and survey and also Pfizer's media room for more information at tinyurl.com/32wdx7m

Failure of bevacizumab in early-stage colon cancer

Daniel Sargent

A randomised phase III trial of patients with stage II and III colon cancer showed no benefit of adding bevacizumab to standard adjuvant oxaliplatin plus fluorouracil and leucovorin. Despite suggestive evidence of a short-term benefit, these data and other similar findings dictate that adjuvant bevacizumab should not be used in colon cancer.

The first definitive evidence of clinical benefit of bevacizumab in metastatic colon cancer was reported in 2001.[1] Since then, this agent has become a standard component of the treatment of multiple tumour types in the setting of advanced cancer. Although bevacizumab has produced variable success across disease entities, its clear activity in patients with stage IV colon cancer logically warranted an evaluation of its efficacy in patients with earlier-stage disease. Adjuvant therapy with fluorouracil-based regimens following surgical resection of stage III colon cancer has been the standard of care for approximately 20 years;[2] in 2003 the addition of oxaliplatin to fluorouracil and leucovorin (a combination called FOLFOX) became the current standard of care in adjuvant colon cancer.[3] Now, Allegra et al.[4] report the first trial testing the addition of bevacizumab to the FOLFOX regimen for patients with stage II and III colon cancer.

In the randomised, multicentre trial of 2672 evaluable patients, no benefit was observed for the addition of bevacizumab to standard FOLFOX for the primary endpoint of disease-free survival.[4] The endpoint chosen was appropriate, as results based on disease-free survival have been demonstrated to be highly predictive of later overall survival findings.[5] The overall trial results are definitive; the possible benefit suggested by the hazard ratio of 0.89 is clearly non-significant (P=0.15). Any modest possible benefit in the initial phase of the trial was attenuated over time; in the period from 2 to 3.5 years of follow-up, the recurrence rate in the bevacizumab arm was in fact higher than in the control arm. In addition, the results of a second trial of bevacizumab in the setting of stage III colon cancer were announced in September 2010.[6] In that trial, the results at three years numerically favoured the control arm (FOLFOX alone). Thus, on the basis of these two trials, bevacizumab is clearly not recommended for the adjuvant treatment of stage II and III colon cancer.

In an exploratory analysis, Allegra et al.[4] identified a possible short-term disease-free survival benefit of bevacizumab in the first 15 months following randomisation. This finding is intriguing, given that the bevacizumab treatment was administered for 12 months. Owing to the potential bias induced by unequal time to imaging between the two arms of the trial (imaging frequency was not protocol mandated), a sensitivity analysis was conducted attempting to adjust for the differential time to first imaging that

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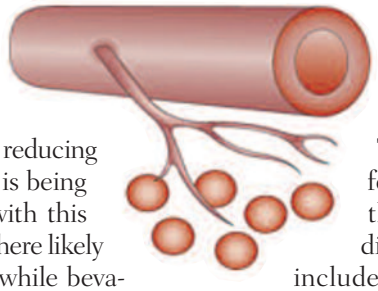
was observed. In this analysis, the short-term benefit of bevacizumab remained, with some attenuation of the first 15 month hazard ratio, from 0.61 to 0.71. Allegra et al.[4] conclude that, all factors considered, this finding likely represents a true biological effect of bevacizumab in reducing recurrence risk while it is being administered. I agree with this conclusion that indeed there likely is a short-term benefit while bevacizumab is being delivered. Whether longer-term bevacizumab exposure would further delay recurrence, eventually eradicate tumour cells and thus prevent recurrence, or have no further effect can only be tested through a subsequent randomised trial. However, given that most stage II and III patients are cured by surgery alone, and considering the adverse effects and inconvenience associated with bevacizumab and the cost, it is unclear whether such a trial could succeed (or even be appropriate) in the stage III setting. A trial of extended-duration bevacizumab in the alternative setting of maintenance therapy for patients with resected stage IV disease, where the recurrence risk is much higher (50%–70% risk of recurrence within two years) may be a more promising alternative.



On the basis of the results reported by Allegra et al.,[4] FOLFOX following surgical resection remains the standard of care for stage III colon cancer. This finding is clearly disappointing, as it represents the third agent with demonstrated activity in stage IV disease that has failed to improve outcomes in earlier-stage disease. Specifically, in addition to bevacizumab, the proven activity of both irinotecan and cetuximab in patients with advanced disease has not translated into benefit in patients with stage III disease.[7,8] As such, it seems the standard paradigm for drug development in this setting is broken: activity in metastatic disease is not a reliable predictor of adjuvant therapy benefit. The biological reasons for this discordance are the subject of intense discussion, possibilities include a different biology between existing visible versus micrometastatic disease (including the concept of epithelial–mesenchymal transition of tumour cells) and the presence of therapy-resistant cancer stem cells. However, the fact remains that we currently do not have an accurate predictor of efficacy for a new proposed adjuvant therapy. A possible alternative approach, the use of neoadjuvant chemotherapy in early-stage disease, seems worthy of exploration. Rectal cancer therapy has moved primarily to the neoadjuvant paradigm (as has much research in breast cancer). The ability to test a therapy's impact in an intact tumour (as well as obtaining pre-treatment and post-treatment biospecimens) is very attractive. Clinical trials of neoadjuvant therapy for colon cancer are ongoing.[9] In the setting of stage II disease, given the high cure rate (approximately 20% recurrence risk), very modest benefit of fluorouracil[10] and no benefit of oxaliplatin,[3] research is focused on strategies for risk assessment to identify patients who are at high risk of recurrence and thus may be considered for adjuvant therapy.

Even if the paradigm of advanced disease testing before adjuvant trials remained appropriate, at the present time there is a dearth of agents in later-stage (phase III) testing in advanced colon cancer. Currently, the most pressing adjuvant therapy question seems to be that of the optimal duration of therapy. On the basis of the cumulative neurological toxic effects of oxaliplatin, reducing the treatment time to three months (from the current six months) would be highly advantageous. This question is being tested in four ongoing trials and one planned randomised trial that are being conducted throughout the world (including the TOSCA trial in Italy, the SCOT trial headquartered in the UK, the C80702 trial in the USA and the PRODIGE/GERCOR trial in France). These trials have prospectively agreed to pool their data for a definitive noninferiority analysis with at least 10,500 patients through the International Duration Evaluation of Adjuvant Chemotherapy (IDEA) collaboration.

In conclusion, the primary clinical implications of the study by Allegra et al.[4] are clear – bevacizumab should not be used in the adjuvant setting in colon cancer outside clinical trials – and at the same time raise many new questions of how to best develop new agents before adjuvant testing. Innovative strategies are needed to assess new agents and treatment strategies, as colon cancer remains a major cause of cancer death worldwide.

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

Practice point

The use of adjuvant bevacizumab in the setting of stage II or III colon cancer is not recommended.

Author affiliations: Division of Biomedical Statistics and Informatics, Mayo Clinic Cancer Center, Rochester, Michigan. *Acknowledgements*: The author would like to thank Axel Grothey for helpful discussions. *Competing interests*: The author declares that he has previously worked as a consultant for Genentech

Ultra-targeted accelerated partial breast irradiation using TARGIT – a cautionary note

Rajiv Sarin

One of the seven ongoing trials of accelerated partial breast irradiation (APBI) has concluded that single-dose intraoperative radiotherapy should be considered as an alternative to protracted whole-breast irradiation. With a median follow up of two years, such conclusions seem premature. Until the risk and pattern of recurrence is reported at longer follow up, APBI should remain experimental.

Accelerated partial breast irradiation (APBI) is an abbreviated radiotherapy course delivered to the tissue surrounding the excision cavity. It is under intense clinical investigation as a therapeutic approach for low-risk early-stage breast cancers.[1] Phase II studies of APBI using multicatheter brachytherapy or external-beam radiotherapy show high local-control rates at 7–12 years median follow up.[2–4] These studies highlight the long natural history of the low-risk early-stage breast cancers for which APBI is being proposed. It therefore seemed prudent to wait for the 5–10 year follow-up data on ~16,000 women enrolled in seven randomised controlled trials comparing APBI with whole-breast irradiation[2] to make definitive conclusions on the safety and efficacy of APBI and to establish the clinical, pathological or technical contexts where caution should be exercised with different APBI techniques.[2] However, the investigators of one of these trials, the TARGIT trial, thought otherwise.

In their report,[5] the TARGIT investigators state that their trial "provides robust and mature evidence... showing that targeted intraoperative radiotherapy is safe," and concluded that, "for

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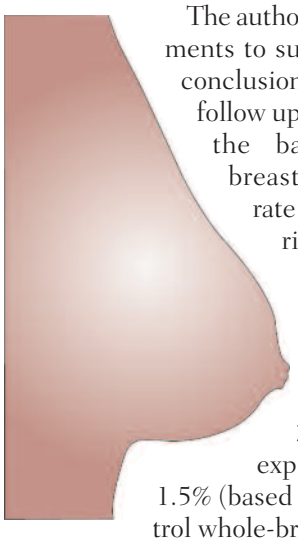
selected patients with early breast cancer, a single dose of radiotherapy delivered at the time of surgery by use of targeted intraoperative radiotherapy should be considered as an alternative to external beam radiotherapy delivered over several weeks." In the accompanying commentary, Azria and Bourgier[6] are convinced that, for elderly patients, "APBI is the new standard and TARGIT is an excellent approach." Furthermore, a lead TARGIT investigator has highlighted that the UK National Health Service wastes £4 million annually on homeopathy, which he argues could be used to provide TARGIT.[7] He goes on to question whether the introduction of TARGIT APBI will have to wait for financial approval while homeopathy continues to creep under the hurdle. Against this backdrop, they argue, the oncology community should take a stand on endorsing the wider use of TARGIT APBI as standard of care for women fulfilling the selection criteria of the TARGIT trial. While this view is endorsed by the TARGIT triallists and other reasearchers,[5–7] I would consider this premature because of issues highlighted in this article.



In the randomised, multicentre TARGIT trial, 2232 women aged ≥45 years with low-risk early-stage breast cancer received intraoperative TARGIT APBI or whole-breast irradiation for 5–7 weeks.[5] At its initiation in 2000, the trial aimed to publish the results in 2006 with median follow up of five years.[8] However, accrual was highly extended and two thirds of the patients were recruited in the last three years of the decade-long accrual. For the whole cohort of randomised patients, the minimum follow-up period is not specified and the median follow up is 25 months. Fewer than 20% of the enrolled patients were followed up beyond four years before publication of the data. The authors have, therefore, restricted the display of local recurrence rates to four years, which was not significantly different between the two arms – local recurrence rate of 1.2% with TARGIT and 0.95% with whole-breast irradiation (P=0.41). From this report, it is not clear if there were any incidences of local recurrence beyond the four-year period.

The authors have used two arguments to support their definitive conclusions, despite such short follow up. First they argue that the background five-year breast cancer recurrence rate in their cohort of low-risk breast cancer patients, which they had projected 10 years ago to be 6% and formed the basis of recruiting 2232 women, is now expected to be around 1.5% (based on data from the control whole-breast irradiation group in the study) and, therefore, only 585 cases are sufficient to prove non-inferiority. In contrast, other prospective APBI studies, such as the MammoSite study,[9] that have discussed results of a subset of their patients having a longer follow up than the whole cohort, have showed the characteristics and treatment variables of this subset, and have refrained from drawing practice-changing conclusions. With a decade-long accrual in the TARGIT trial,[5] the characteristics of patients, disease and treatment may have changed during the trial period and it should be seen how representative they are of the entire enrolled population of 2232 women. Vaidya et al.[5] argue that a quarter of the 2232 enrolled patients are sufficient to draw conclusions on noninferiority; however, no mention is made about the international steering committee of the TARGIT trial increasing the sample size from 2232 to 3432 women in March 2010.[10] The second argument is that the short follow-up period covers the peak hazard of local recurrence that occurs between two and three years after surgery, allowing them to draw cautious yet reasonable conclusions about efficacy. Yet prospective studies on similar low-risk patients treated with quality-assured APBI have shown that actual breast cancer recurrence rates increase with time. For example, the German–Austrian ESTRO phase II trial[4] that assessed 273 patients with a median 63 months follow up showed that a negligible four-year breast cancer-recurrence rate, similar to the present TARGIT report, equated to a recurrence rate of 2.3% at five years and 5% at eight years. Moreover, in women with a nonhomogeneous dose of radiation, the eight-year recurrence rate was 7.5%. If the TARGIT trial with just 212 women at risk at four years after intraoperative APBI can draw reasonable conclusions on efficacy, many other ongoing or recently concluded randomised trials of APBI would be better placed to draw similar conclusions without any further wait.

When mature data are presented from the TARGIT study, interpretation should acknowledge that 234 out of 1113 women (21%) in the TARGIT APBI cohort received treatment in the form of mastectomy or whole-breast radiotherapy either because of protocol violation or adverse pathology.[5] The primary analysis has been performed on an intention-to-treat basis, as recommended by the CONSORT guidelines. However, with one in five women

in the TARGIT arm undergoing standard treatment, the effect of TARGIT APBI may have been overestimated. It would be important to know the median follow up in the women who received TARGIT APBI without whole-breast radiotherapy and the number and site of breast cancer recurrences in this cohort at clinically appropriate time points.

Based on radiobiological modelling, Vaidya et al.[5] suggest that the biological dose from TARGIT 50 kV X-rays will be 20%–30% higher than the physical dose. Assuming this is true, it means that at 1 cm from the excision cavity the physical dose equivalent is only 7 Gy. If the long-term results of TARGIT show that a single dose of 20 Gy at the surface and 5–7 Gy at a depth of 1 cm is able to control breast cancer, it would imply that either the volume of tissue that needs full-dose irradiation is a few millimetres or that the low dose of radiation at 1 cm, which we otherwise consider subtherapeutic, is sufficient to control cancer. Such findings would have far-reaching implications for cancer treatment with adjuvant radiotherapy. If the low physical dose of 5 Gy at 1 cm with TARGIT is radiobiologically a much higher dose and sufficient to control cancer then it can also be expected to correlate with late toxic effects, especially in the 142 women who received full-dose conventional whole-breast irradiation following full-dose TARGIT. The absence of reported incidences of fat necrosis in the Vaidya et al.[5] study is unusual for an APBI series. Without knowing the compliance with annual mammography during follow up, site of recurrence and its distance from the lumpectomy site, the possibility of under-reporting of breast cancer recurrence cannot be ruled out. Imaging of another spherical device placed intraoperatively in the excision cavity has shown that in some instances there could be a significant gap between the surface of the applicator and the breast tissue.[1] As TARGIT is an ultra-targeted form of radiotherapy with very sharp fall off of the radiation dose and is delivered in a single sitting, placement precision and its verification is crucial. Even a few millimetres of fluid between the applicator surface and excision cavity wall would seriously compromise the absorbed dose with 50 kV X-ray.

Trials evaluating new adjuvant therapy in early-stage breast cancer refrain from reporting results at very short median follow up, without clearly indicating them as interim results, and do not make practice-changing conclusions at these interim time points. Leading publications with definitive therapeutic recommendations based on selective discussion on a subgroup of less than 20% of patients with a four-year follow up is a new phenomenon in early-stage breast cancer. This requires all triallists, reviewers and editors to take a clear stand. I fear that the premature report[5] with definitive conclusions, accompanying supportive commentary[6] and correspondence in a leading medical journal, and associated media coverage, may trigger a race to report the remaining six APBI trials prematurely.

Most of these trials already have much longer median follow up than the TARGIT trial and if the statistical rationale proposed for early reporting and drawing definitive conclusions are accepted for the TARGIT trial, they will be applicable to almost all the remaining trials.

There is no doubt that APBI is approaching a very exciting phase and has real potential to offer safe, convenient and cost-effective breast conservation in the coming decade. But when dealing with a low-risk disease with long natural history, premature conclusions can sometimes be counterproductive.

References

1. R Sarin (2005) Partial-breast treatment for early breast cancer: emergence of a new paradigm. *Nat Clin Pract Oncol* 2:40–47
2. M Mannino and J Yarnold (2009) Accelerated partial breast irradiation trials: diversity in rationale and design. *Radiother Oncol* 91:16–22
3. BV Offersen, M Overgaard, N Kroman et al. (2009) Accelerated partial breast irradiation as part of breast conserving therapy of early breast carcinoma: a systematic review. *Radiother Oncol* 90:1–13
4. V Strnad et al. (2010) Accelerated partial breast irradiation: 5-year results of the German–Austrian multicenter phase II trial using interstitial multicatheter brachytherapy alone after breast-conserving surgery. *Int J Radiat Oncol Biol Phys.* doi: 10.1016/ijrobp.2010.01.020
5. JS Vaidya et al. (2010) Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. *Lancet* 376:91–102
6. D Azria and C Bourgier. (2010) Partial breast irradiation: new standard for selected patients. *Lancet* 376:71–72
7. M Baum. (2010) Homoeopathy waives the rules. *Lancet* 376:577
8. Lancet. (2010) Protocol 99PRT/47 targeted intraoperative radiotherapy (Targit) for breast cancer. www.thelancet.com/protocol-reviews/99PRT-47
9. JC Nelson et al. (2009) Four-year clinical update from the American Society of Breast Surgeons MammoSite brachytherapy trial. *Am J Surg* 198:83–91
10. NIHR Health Technology Assessment Programme. (2010) TARGIT protocol version 5.0, April 2010. http://www.hta.ac.uk/protocols/200700600049.pdf

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NEWSROUND

Selected reports edited by Janet Fricker

Low-dose aspirin reduces death from several cancers

→ The Lancet

Daily aspirin reduced deaths due to any cancer by 20%, reports a meta-analysis study, but the benefits only really became apparent after patients had been taking the drug for five years or more.

While earlier studies have suggested that long-term aspirin therapy may protect against colon cancer, the current study led by Peter Rothwell, of the Department of Clinical Neurology at Oxford University, is the first to show that aspirin protects against other cancers, such as oesophageal, gastrointestinal, lung, brain and pancreatic cancers.

Several lines of evidence have suggested that long-term use of aspirin might reduce the risk of some cancers, particularly gastrointestinal tumours. In animal models aspirin reduces incidence or growth rate or both of several cancers, mediated by inhibition of the cyclo-oxygenase enzymes and production of prostaglandins and other inflammatory mediators. Observational studies in humans have also suggested that aspirin reduces the risk of certain cancers. In an earlier study, published in the *Lancet* in October 2010, Rothwell and colleagues showed that long-term low-dose aspirin (75 mg per day) reduced death rates from colorectal cancer by more than a third. In the current research the team studied deaths due to all cancers.

The meta-analysis identified eight randomised trials of daily aspirin versus no aspirin, including 25,570 patients, that had originally been undertaken to look at primary or secondary prevention of vascular events. Doses of aspirin in the eight trials ranged from 75 mg to 500 mg per day. Altogether 674 patients died from cancer in the course of the studies.

Results showed that during the period of the clinical trials, which lasted for about four years, allocation to the aspirin group reduced the risk of death from cancer by 21% (P=0.003).

On analysis of individual patient data, available from seven trials involving 23,535 patients, it became apparent that benefits increased with time. After five years the risk of all cancers was reduced by 34% (P=0.003) and the risk of gastrointestinal cancers by 54% (P=0.003).

The researchers also wanted to determine whether the benefits from aspirin continued over time, and this was made possible by the three UK-based trials that had continued to obtain data for deaths due to cancer after completion of the trials via the national death certification and cancer registration systems.

At 20 years follow-up the three trials showed that the risk of cancer death remained 20% lower for all solid cancers (P<0.0001) and 35% lower for gastrointestinal cancers (P<0.0001) among the participants taking aspirin. When the fall in risk of death was broken down according to individual types of cancer, it was 60% for oesophageal cancers, 40% for colorectal cancer, 30% for lung cancer and 10% for prostate cancer. Reductions in pancreatic, stomach and brain cancers were difficult to quantify due to the small number of deaths. Taking larger doses of aspirin and smoking and gender had no effect on the results.

The authors, from Oxford, Edinburgh and Japan, conclude, "These findings provide the first proof in man that aspirin reduces deaths due to several common cancers. Benefit was consistent across the different trial populations, suggesting that the findings are likely to be generalisable."

When weighing up the risk and benefits of taking aspirin, they add, clinicians will now need to consider the protective effects against cancer. "Although the reduction in risk of

ischaemic vascular events on aspirin in healthy individuals is partly offset by a small increase in risk of non-fatal bleeding complications, the balance of risk and benefit will now be altered by the reduction in cancer deaths after five years' treatment. Our analyses show that taking aspirin daily for 5 to 10 years would reduce all-cause mortality (including any fatal bleeds) during that time by about 10%."

Limitations of the study, write the authors, include the fact that it only used trials of daily aspirin, that too few women had been recruited to allow the investigators to determine the effects of aspirin on gynaecological cancers, and that they were unable to determine the effect of continued aspirin use after 20 years.

The next step, say the authors, will be to explore whether there is any protective effect of aspirin on the incidence or progression of cancer.

■ P Rothwell, F Fowkes, J Belch et al. Effect of daily aspirin on long-term risk of death due to cancer: analysis of individual patient data from randomised trials. *Lancet* 7 December 2010, doi:10.1016/S0140-6736(10)62110-1

Radiation therapy for head and neck cancer leads to hearing loss

➜ Arch Otolaryngol Head Neck Surg

Patients who have undergone radiotherapy for head and neck cancers experience a higher incidence of hearing loss and more severe hearing handicaps than age-matched controls who do not have cancer, reports a Brazilian study.

Treatments for head and neck cancer, including surgery, chemotherapy and radiotherapy, either alone or in combination, are all known to affect the auditory system and cause temporary or permanent hearing loss. With radiotherapy, when the inner ear is included in the irradiation field, permanent sensorineural hearing loss may result from the loss of ciliated cells in the cochlea, with latency periods ranging from 1.5 to 5 years.

In the current study, Christiane Schultz and colleagues, from the Hospital de Câncer de Barretos (Barretos, Brazil), set out to investigate hearing difficulties among 141 patients with head and neck cancer who had undergone radiotherapy alone or in association with chemotherapy or surgery. The patients, together with 141 age-matched controls (who had never undergone oncological treatment placing their hearing at risk), underwent hearing evaluations and completed the Hearing Handicap Inventory for the Elderly (HHIE) questionnaire, which assessed the effect of hearing loss on their lives. The degree of hearing handicap was divided into three categories according to severity.

Results show that hearing loss was detected in 103 (73.3%) of participants exposed to radiation therapy versus 69 (48.9%) of age-matched controls ($P<0.001$). Severe or profound hearing loss occurred in 6.4% of right ears and 8.5% of left ears in the radiation-treated group, as compared with 0.7% of right ears and 1.4% left ears of control participants.

Hearing loss was mostly sensorineural (resulting from disorders or damage involving the nerves or the inner ear) as opposed to conductive (resulting from interference in sound transmission, usually involving the outer or middle ear).

Furthermore, 19.1% of patients in the radiation treatment group had suffered a severe hearing handicap versus 2.8% in the control group ($P<0.001$). "This indicates that, when present, hearing losses were substantially greater and more incapacitating after the radiotherapy," write the authors.

There was also found to be a correlation between the degree of hearing loss and score on the HHIE questionnaire, with participants whose hearing loss went untreated being more likely to report feeling lonely, depressed, worried, anxious or paranoid, and to have fewer social activities and be less able to process information about their environments.

"This is extremely important because behavioural patterns that are more depressive or that present greater tendencies for social isolation can sometimes be attributed to the cancer or to the functional sequelae of the treatment. Nonetheless, one must remember that hearing loss and hearing handicap may also lead to such behaviour," write the authors.

They conclude that in order to enable better rehabilitation of patients with head and neck cancer, hearing loss should form part of the investigations.

■ S Schultz, M Goffi-Gomez, P Liberman et al. Hearing loss and complaint in patients with head and neck cancer treated with radiotherapy. *Arch Otolaryngol Head Neck Surg* November 2010, 136:1065–1069

Combination therapy shows promise in biliary tract cancer

➜ Lancet Oncology

Cetuximab in combination with gemcitabine and oxaliplatin produced encouraging results as a first-line palliative care treatment in patients with biliary cancer. The Austrian single-centre study found that the addition of cetuximab was associated with increased response, substantial tumour shrinkage and the potential for secondary resection.

Patients with biliary tract cancer have a poor prognosis, with an overall survival that is less than 15% at five years. The only curative treatment is surgical resection, but even after surgical resection recurrence is frequently reported and until recently no standard palliative chemotherapy had been defined. Two phase III trials have recently shown that gemcitabine plus cisplatin (GEMCIS) or oxaliplatin (GEMOX) are superior in terms of overall survival to gemcitabine alone.

The current phase II study by Birgit Gruenberger and colleagues, from Barmherziger Brüder Hospital Vienna, Austria, set out to investigate the efficacy and safety of adding

cetuximab to the GEMOX combination. Cetuximab is a targeted therapy directed against the epithelial growth factor receptor (EGFR), which has been associated with improved outcome for malignancies including colorectal, lung and head and neck cancer.

Between October 2006 and July 2008, 30 patients with unresectable biliary tract cancer were enrolled from one centre in Austria. All patients received 500 mg/m^2 cetuximab as a two-hour intravenous infusion on day 1, and 100 mg/m^2 oxaliplatin on day 2, every two weeks for 12 cycles. The primary outcome was overall response rate.

The investigators found that 19 (63%) of the patients experienced objective response – three (10%) achieved complete response and 16 (53%) achieved partial response. Following major response to therapy, nine patients (30%) were able to undergo secondary curative resection. Of this subgroup, five had intrahepatic cholangiocarcinoma that had initially not been amenable to secondary resection, and four presented with locally advanced extrahepatic tumours that had been unresectable due to vascular involvement. Grade 3 adverse events such as skin rash, peripheral neuropathy and thrombocytopenia occurred in 13 patients, but none reported grade 4 events.

The authors write that comparisons of these results with response rates achieved in other studies verified that cetuximab plus GEMOX has a better overall response rate than gemcitabine alone, GEMOX alone, or other chemotherapy combinations.

Following findings in studies of metastatic colorectal cancer, the association between KRAS mutation status and response to cetuximab was also investigated. KRAS mutations were detected in three out of 30 patients, but did not appear to preclude benefit from combined cetuximab and GEMOX. Patients with KRAS mutated tumours had a shorter median survival than did those with wild-type tumours (1.67 vs 7.67 months, P=0.071).

The authors conclude, "This combination treatment had an acceptable toxicity profile and resulted in potentially curative secondary resection in a third of patients, which significantly lengthened progression-free survival. These findings provide justification for further studies of this treatment combination in a randomised study of a large cohort."

In an accompanying commentary, David Malka, Valérie Bogie and Michel Ducreux, from the Institut Gustave Roussy (Villejuif, France), cautioned that small, single-centre studies can be prone to selection bias, giving the example that 97% of patients in the current study had an Eastern Cooperative Oncology Group performance status of 0–1. Furthermore, they added, several previous reports have found KRAS mutation rates in biliary cancers to be higher than recorded in the current study. "Hence, data from large prospective cohorts are needed to specify the actual prevalence of KRAS mutations – and BRAF mutations . . . and establish whether these mutations are predictive for inefficacy of anti-EGFR antibodies in patients with advanced biliary cancers."

■ B Gruenberger, J Schueller, U Heubrandtner et al. Cetuximab, gemcitabine, and oxaliplatin in patients with unresectable advanced or metastatic biliary tract cancer: a phase 2 study. *Lancet Oncol* December 2010, 11:1142–1148

■ D Malka, V Boige and M Ducreux. Biliary cancers, chemotherapy, and cetuximab. *ibid* pp 1110–1111

New standard of care defined in multiple myeloma

→ The Lancet

The addition of bortezomib to standard induction therapy (thalidomide plus dexamethasone) prior to double autologous stem cell transplantation in patients with newly diagnosed multiple myeloma improved the rate of complete or near-complete response almost three fold, a landmark study from the GIMEMA Myeloma Network has found. The researchers, led by Michele Cavo from the University of Bologna, Italy, concluded that triple therapy induction represents a new standard of care for patients with multiple myeloma eligible for transplant.

Thalidomide, bortezomib and lenalidomide have greatly advanced myeloma treatment during the past decade, with the thalidomide plus dexamethasone induction regimen (TD) showing the highest activity and being acknowledged as the new standard of care for induction therapy in the US. However, small studies have suggested that the addition of bortezomib to TD (VTD) may result in increased rates of high-quality responses for all phases of myeloma.

Cavo and colleagues undertook a phase III study to assess the efficacy and safety of VTD versus TD as induction therapy in preparation for double autologous stem-cell transplantation in newly diagnosed multiple myeloma patients. Altogether 480 patients aged 18 to 65 from 73 sites in Italy with previously untreated symptomatic myeloma were randomly assigned to receive VTD (n=241) or TD (n=239). The intention to treat analysis included 236 patients in the VTD arm and 238 in the TD arm.

Results showed that 31% of patients in the VTD arm achieved complete or near-complete response compared with 11% of patients in the TD arm (P<0.0001). Furthermore, the median time to best complete response was 9 months in the VTD arm versus 14 months in the TD arm (P<0.0001).

Patients in the VTD arm had a 29% three-year probability of progression or relapse compared with 39% for patients in the TD arm (P=0.0061).

However, on the down side, 56% (n=132) of patients in the VTD arm experienced grade 3 or 4 adverse events compared with 33% (n=79) in the TD arm (P<0.000). Additionally, 10% of patients on VTD experienced peripheral neuropathy compared with 2% on TD (P=0.0004). The study showed no significant differences in stem-cell collection between the two arms.

Despite the high levels of peripheral neuropathy, only one patient experienced grade 4

peripheral neuropathy and only two patients discontinued treatment due to toxic effects.

"Induction therapy with VTD was associated with a significantly higher rate of complete or near complete response than was induction therapy with TD. Therefore, VTD represents a new standard of care to maximise the degree and speed of tumour reduction in patients with myeloma who are eligible for transplant," conclude the authors.

Commenting on the finding that no difference in overall survival was found between the two groups, the authors speculate that the follow-up period may have been too short to detect differences, that the sample size may have been too small and that the increasing availability of effective treatments at time of relapse may have confounded any meaningful analysis of studies in first-line treatment.

In an accompanying commentary, Paul Richardson, from Harvard Medical School, writes, "The unprecedented high quality of responses engendered by these combinations with a generally favourable safety profile bodes well for continued benefit to patients, with yet further improvements in outcome still needed for this otherwise incurable malignancy."

The significant neurotoxicity encountered with VTD, he adds, contrasts with an "otherwise promising picture". Strategies to reduce toxicity include use of less neurotoxic but active combinations of drugs such as lenalidomide and dexamethasone, or lowering doses of bortezomib and thalidomide.

The question of whether additional drugs should be added to the three-drug induction strategy (such as monoclonal antibodies, histone deacetylase inhibitors, heat shock protein-90 inhibitors) also requires further consideration, Richardson writes.

A study is currently underway by the European Myeloma Network to address whether novel agents might delay or challenge the need for autologous stem cell transplantation in myeloma.

■ M Cavo, P Tacchhetti, F Patriarca et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. *Lancet* 18 December 2010, 376:2075–2085

■ P Richardson. A new standard of care in newly diagnosed multiple myeloma. *ibid* pp 2043–2044

Docetaxel sets new standard of care in operable, high-risk node-negative breast cancer

➜ New England Journal of Medicine

For women with operable, high-risk node-negative, early-stage breast cancer, adjuvant treatment with the drug combination of docetaxel, doxorubicin and cyclophosphamide (TAC) reduced the risk of recurrence by 32% compared with the traditional treatment approach of fluorouracil, doxorubicin and cyclophosphamide (FAC), reports a study from the Spanish Breast Cancer Research Group (GEICAM).

"Our findings… show that TAC is effective both in patients with node-positive and in those with high-risk node-negative early-stage breast cancer," write the authors, led by Miguel Martin from the Hospital General Universitario Gregorio Marañón in Madrid.

Although adjuvant taxane-based regimens are now the standard of care for patients with node-positive early-stage breast cancer, their efficacy in patients with high-risk node-negative disease has not been defined. The benefits of adjuvant chemotherapy in the node-negative populations have, however, been well established.

In the open-label phase III GEICAM 9805 study, between June 1999 and March 2003, 1060 women with axillary-node-negative breast cancer and at least one high-risk factor for recurrence were randomised to treatment with either TAC (n=539) or FAC (n=521) for six cycles every three weeks, following surgery. The study was funded by Sanofi-Aventis (makers of docetaxel) and involved 40 centres in Spain, four in Germany and two in Poland.

Results show that at a median follow-up of 77 months, 87.8% of the women were alive and disease-free in the TAC group compared to 81.8% in the FAC group (HR 0.68, 95% CI 0.49–0.93; P=0.01). The benefit was consistent across subgroups regardless of hormone receptor status, HER2 status, menopausal status, age, tumour size or histologic grade. On the basis of the trial, the number of patients who would need to be treated to prevent recurrence in one patient is 17, write the authors.

The difference in survival – 95.2% for TAC and 93.5% for FAC – was not significant (HR 0.76; 95% CI 0.45–1.26; P=0.29). This, the authors suggest, was because the number of deaths was small (26 vs 34). The rates of grade 3 or 4 adverse events were 28.2% with TAC and 17.0% with FAC (P<0.0001), and serious adverse events were recorded in 4.7% of the women in the TAC group compared to 0.8% in the FAC group.

"The small number of deaths occurring at the time of the analysis indicates that a longer follow-up period will be needed to assess survival among patients with node-negative breast cancer as compared with those who have node-positive disease," write the authors.

"The GEICAM 9805 trial shows the effectiveness of an adjuvant taxane-based regimen over a non-taxane-based regimen in a population of patients with axillary, lymph-node-negative, early-stage breast cancer," they conclude, adding that the acute toxic effects associated with TAC are manageable when treatment is combined with granulocyte colony-stimulating factor introduced as primary prophylaxis.

The benefit of TAC over FAC in premenopausal women, speculate the authors, may be partly due to its ability to induce amenorrhoea in more women.

■ M Martín, M Seguí, A Antó et al. Adjuvant docetaxel for high-risk, node-negative breast cancer. *NEJM* 2 December 2010, 363:2200–2210

An advanced oncology degree for busy specialists across the globe

Peter McIntyre

Oncologists who want to develop and work to their full potential can find it hard to balance the competing priorities of clinical practice and academic study. For some of them, wherever in the world they may be based, this new online MSc in Advanced Oncology run by the University of Ulm may be the answer.

It is always early morning somewhere in the world! And somewhere a busy cancer doctor or scientist is up extra early and logging on to a site in Germany before they head off to their own clinic or laboratory. As they drink their tea or coffee, they view a lecture by one of the experts from the University of Ulm and they look over their notes as they take the bus or train to work.

These are the first students to undertake an online Master of Science in Advanced Oncology – now well into their second semester at the University of Ulm, but physically somewhere else completely.

The 18 students are doctors or scientists specialising in haematology and oncology and working in cancer centres from Brazil, Egypt, Iraq, Moldova, Romania, Nigeria and South Africa, to Germany, Italy and USA. Numbered among them are some scientists working for pharmaceutical companies who need to learn more about cancer therapy and trials.

The two-year course is run from the International Center for Advanced Studies in Health Sciences and Services (ICAS) at Ulm University. Medical director Manuela Bergmann, an oncologist and haematologist, designed the course to fill a gap in postgraduate training, to "export knowledge" and to help students become leaders of cancer services in their own countries.

"It is a study programme for people who are very engaged in their profession and are all experts. The major problem in such a group is time management. They need to be up to date but they cannot afford to go to seminars and be out of the office for more than one week. So far as I know, no country in the world offers a curriculum online where you get an organised structure with the latest level of knowledge. We tried to find a solution for time management and a structure for organised knowledge."

Each semester has 60–70 lectures, which the students follow at their own pace. In addition they attend one-week seminars ('summer schools') five times each year, where they meet their lecturers and fellow students.

There are six modules in all. The four online modules cover interdisciplinary oncology (including cellular and molecular biology), clinical research (including ethical aspects and management of trials), advanced therapies and management. The management module prepares doctors to run a department, using lecturers from the Institute of Business at Ulm University and from McKinsey consultants. Katarina Janus, professor of healthcare management at Ulm and a pioneer of research into what motivates doctors to work most effectively, also teaches on this module.

The lectures themselves are interactive – with opportunities to leave questions for the lecturer and get a response,

UNIVERSITY OF ULM

The class of 2010. The first intake of 18 doctors and scientists come from 10 countries across the globe, and are pictured here at one of the week-long seminars that supplement the predominantly online course work

usually within 24 hours. There is also a link up with the European School of Oncology (ESO) – which is also the publisher of *Cancer World* – under which students can attend the weekly online live e-grandround sessions (www.e-eso.net). At the end of their two-year course they also attend the week-long Masterclass in Oncology run jointly by ESO and ESMO (European Society for Medical Oncology), which is designed for future leaders of oncology.

The two-year course costs almost €20,000 plus travel and accommodation for the five attendance weeks. While a few students cover their own fees, most are supported by their employers (in the case of the pharmaceutical companies) or by charitable foundations. ESO supports two of the 2010–2011 intake and will support one of the dozen who will join them in October 2011.

Most of those on the course are in their 40s. Ahmed Rabea, assistant lecturer at the National Cancer Institute in Cairo, where he specialises in malignant haematology, is the youngest at just 29 years old.

"They have been encouraging older people in higher positions to do the course. I was amazed and really happy that I was accepted," he says. Ahmed was still more delighted to be awarded an ESO bursary. "I would not be able to afford this course if I were not supported by ESO. They are paying for everything, the course, travelling, accommodation, everything."

"I believe we can change the way we treat the patients with a better outcome if we have been taught well with

"Clinical oncology is highly dynamic and requires almost continuous medical education"

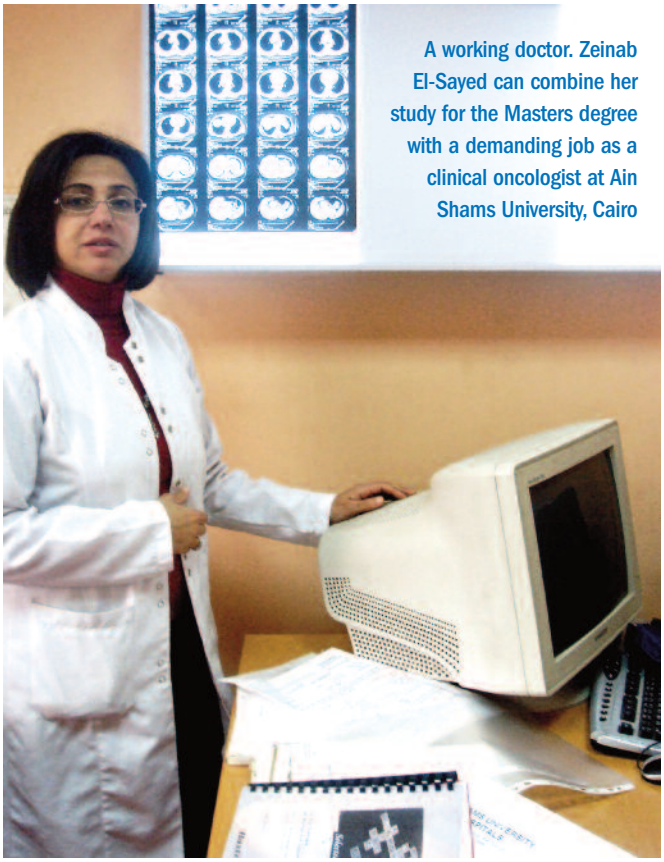
the newest modalities and try to apply that in our job. I know there is a problem in Egypt with financial support, but if we are taught to conduct proper experiments and trials we can supply our patient with the proper medication. It will give me an idea about the best way to deliver knowledge and update junior residents. It has also opened a lot of opportunities for contact with physicians from all over the world, and this may be a seed for future collaboration."

For the first semester, when he was completing a fellowship at Princess Margaret Hospital, Toronto, Canada, Ahmed would listen to lectures before he went to work and make up time at the weekend. In Cairo things are tougher, since he works six days a week until all the patients have been seen, which can be as late as midnight. He is confident, however, that he will finish the course successfully. "I am really happy with this programme and I am eager to finish it because it will do a lot for me. I know I can do it."

The other ESO bursary went to Zeinab El-Sayed, assistant professor at the Department of Clinical Oncology at Ain Shams University, Cairo, where she specialises in head and neck cancers, sarcomas, paediatric oncology and cancer of unknown origin.

"I obtained my MD in 1999, but clinical oncology is highly dynamic and requires almost continuous medical education. It is not the same as it was 10 years ago. When I saw the modules and the curriculum, I found this course very attractive." A visit to Ulm convinced her that the course was right. "It was very impressive. I found the staff very cooperative. The other students are a very nice group. I was very happy and felt I had made the right choice."

She rises early to do her studying, and makes up time at the weekend, as she ensures that her two boys, aged 16 and 11, are also doing their homework!



A working doctor. Zeinab El-Sayed can combine her study for the Masters degree with a demanding job as a clinical oncologist at Ain Shams University, Cairo

Course organisers can see how much time each student spends on line, but the acid test is not the hours of work but passing the exams in each module. There is no requirement to study a lecture if this is an area where a student is already strong. Manuela Bergmann says, "The students can decide themselves where they have difficulties and have to do more, and where they have less to learn. It is up to them."

Chatrina Melcher, coordinator at the European School of Oncology, said that ESO was backing the course because of its sound structure and innovative approach. "The Master Online Advanced Oncology programme stands out for its impressive and very well structured contents and because it provides academic recognition. It is an excellent example of blending traditional attendance seminars with e-learning, which we felt is an innovative approach."

This course does not admit nurses or younger doctors who have just qualified. However, Manuela Bergmann says that adding new courses will be considered when this one has proved its worth. Applications for the 2011 intake can be obtained from her at Ulm by writing to icas@uni-ulm.de. The closing date for applications is 15 May 2011.