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Learning to care

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Education & knowledge through people & facts

Angelo Di Leo

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Is it safe, is it tolerable? Why not ask the patients?

Kathy Redmond ■ EDITOR

A thought-provoking perspective by oncologist Ethan Basch, published recently in the *New England Journal of Medicine*, highlighted the absence of any patient input into establishing a drug's safety. This might seem surprising, given that distressing symptoms – which patients are best placed to report on – account for a large number of drug-related side-effects.

We know that all too often there is a disconnect between patients' and clinicians' estimates of symptom severity, with patients tending to report symptoms earlier and more frequently than physicians. By failing to collect information on patients' first-hand experience of adverse events we risk systematically underestimating a drug's safety and tolerability.

As Basch and others have argued, this issue is becoming increasingly important with greater use of targeted therapies, which are associated with mild to moderate side-effects that can persist in the long term. These types of therapy are typically reported to be 'well-tolerated' and the harmful impact of their side-effects – including treatment non-adherence – are often overlooked.

The US National Cancer Institute's CTCAE – the adverse events grading system most commonly used in cancer clinical trials – was developed in an era when cytotoxic drugs were administered intermittently and were associated with transient side-effects. There is a big difference between the tolerability of a grade 3 or 4 side-effect that lasts two days and a side-effect that may be less severe but persists in the long term. Using instruments that capture the patient experience – such as the Patient-Reported Outcomes version of the CTCAE – would help throw light on the true impact of persistent, low-grade side-effects and provide greater clarity for the development of triggers for treatment modifications.

The use of existing information technologies, such as mobile-phone-based symptom management systems, could mimimise the additional administrative burdens on clinical trials. This would also help address another limitation of the current approach to collecting data on adverse events, in that patients can report the information when they experience the problem or soon after, rather than reporting back only during clinic visits, where their recall can be subject to distortion by a variety of factors.

Collecting information directly from patients about the side-effects they are experiencing could provide valuable insight into the safety and tolerability of a particular drug and help differentiate it from other similar products.

Patients deserve a voice in defining how tolerable a drug is, and the time is right to correct an anomalous situation in which our knowledge of a drug's side-effects is based too much on second-hand impressions.

The Missing Voice of Patients in Drug-Safety Reporting, by Ethan Basch, can be accessed at http://content.nejm.org/cgi/reprint/362/10/865.pdf

Angelo Di Leo:

mapping the geography of breast cancer

Marc Beishon

Angelo Di Leo cut his research teeth on early studies into personalising chemotherapy. Mapping the geography of interconnected biomarkers that can predict which breast cancer patients respond to what is not a guiding principle for Di Leo so much as an immediate task – a task that he feels would progress far faster were less effort wasted on trials that fail to address differences in tumour biology.

The hottest topic in cancer has for some time been personalising treatment for patients, and interest continues to be fuelled by the explosion in new biological data now feeding into thousands of research programmes around the world. Breast cancer has long led this field, and many experts are predicting major breakthroughs in treatment planning thanks to technologies such as genomic profiling.

But as *Cancer World* has often reported, the complexity of this genetic information alone is enormous. And what we are learning now about the structure and subtypes of tumours is adding yet more layers of complexity says Angelo Di Leo, one of the new wave of top breast cancer clinicians.

"We have of course known for some time that one patient may have a different type of breast cancer from another, but we are now finding that a tumour in one person has different parts that do not play the same role in the life of the cancer. We also know that parts of tumours interact with the host in different ways and can also change over time according to the treatments we give. It's an extraordinarily complex system."

Di Leo, who chairs the oncology department at Prato Hospital in Tuscany, Italy, is a medical oncologist who worked on the first efforts to personalise cytotoxic chemotherapy treatment in the late 1990s, and is now one of the leading international authorities on where the most promising avenues lie, and he is optimistic. "Despite the complexity, I do not believe we have reached a plateau in progress with breast cancer, and with other tumours for that matter," he says. "The biological information will allow us to make substantial improvements in targeting."

He and his team are involved in much of the cutting-edge research into breast cancer, not only studying the latest targeted biological agents, but exploring fields that could help better target these new therapies, such as metabolomics, the study of compounds arising from metabolism, which could give rise to new biomarkers for cancer types. But Di Leo has largely made his name in the field of targeted chemotherapy – finding out which patients benefit most from many existing cytotoxic drugs –

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and he considers we are in a position to uncover much more information about where they can best be applied, alone or in combination with newer technologies, including by going back to data from hundreds of thousands of women who participated in trials that did not – or could not – take into account the biological information we have now.

What is helping Di Leo make his case is having his own oncology unit that he started from scratch in 2003. Up until then, Prato – a city often bypassed in favour of the more glamorous, nearby Florence – had little integrated cancer care to offer patients. After working in Belgium for a long spell, Di Leo took an opportunity to build a new research-oriented oncology department on his return to Italy, rather than take a number two position in a larger, established centre. "The Italian Association for Cancer Research (AIRC), the major funding agency in Italy supporting investigator-driven research, played a critical role in facilitating my programme in Prato. I am also thankful to the Sandro Pitigliani Foundation, which has supported this project since September 2003 even though we were at the beginning of this new venture in Prato."

Given a budget to set up his own vision of an oncology department – and despite inevitable Italian bureaucracy – Prato now has multidisciplinary teams for several cancer types, and a particular strength in breast cancer, as well as a translational research lab. It is also part of a growing regional network – the Tuscan Cancer Institute (Istituto Toscano Tumori). None of this existed a few years ago and it is now a platform for not only enhancing patient care but also developing the careers of young oncologists (Di Leo also has a teaching position at Florence University), and has put Prato on the oncology research map. Oncologists at the Sandro Pitigliani medical oncology unit, Di Leo's key creation, are now regular contributors to major journals and make presentations at top conferences.

"Personalisation is also about taking into account the health and preferences of a patient"

Enthusiasm and experience. Di Leo is very proud of the team he has built up in Prato, and has high hopes of attracting back some of Italy's brightest and best who are currently working abroad

Di Leo confesses to great pride in the team he heads. "It is a perfect example of integration between senior and junior people, who bring either experience or enthusiasm to our programmes. Together with my colleague Augusto Giannini (head of pathology) we are now trying to facilitate the 'return' of bright Italian scientists who have been working abroad for some years." Libero Santarpia, a young pathologist with expertise in genomics, is one such returnee, who recently joined Di Leo's team as leader of the translational research unit, after spending five years at the MD Anderson Cancer Center.

But personalisation is about much more than just the biological behaviour of a tumour – it's also about taking into account the health and preferences of a patient, as Di Leo stresses. "People come up to me in conferences and ask, 'What is the first-line treatment for metastatic breast cancer?' I say, 'I don't know – it depends on the patient in front of you.' You can't possibly map out an algorithm for late-stage disease as there are so many variables, such as the patient's preferences for the level of aggressiveness of treatment, how and when drugs are taken, whether they can tolerate hair loss and other side-effects, and so on. You might just be able to do it for early-stage cancer but for metastatic disease it's impossible."

And communication with patients – especially the first appointment, where impressions are made – can be critical in determining the success of treatment, adds Di Leo, who holds strong views about the quality of doctor–patient interactions. His own career path, he says, has been very helpful in learning the

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craft of the medical oncologist from this standpoint and other aspects of basic clinical work, as well as the research which he subsequently became heavily involved with.

He had the usual motivation for wanting to enter medicine – a desire to help people. "But I was also fascinated by the biological aspects, the complex mechanisms that regulate the body. Oncology is a natural choice for combining these interests." After completing a degree in medicine and surgery at the University of Palermo, he went to work at the National Cancer Institute in Milan in 1989, while also gaining a postgraduate diploma in medical oncology at the University of Pavia.

"My first priority in Milan was to understand how to be a good medical oncologist and provide a good level of care to cancer patients with all tumour types – you can be the brightest clinician around but you have to learn how to communicate with patients. I think also that it is mistake to specialise too early in your career – it's much better to cover different areas of medical oncology and develop a transferable platform – a methodology you can apply to any setting."

Di Leo is concerned too, like many medical oncologists, about the lack of standardisation of training and practice for the specialty around Europe. "Despite the efforts of ESMO [European Society for Medical Oncology] with its certification scheme, it's had little impact on the very mixed picture we see, such as clinical oncologists also carrying our radiotherapy in northern Europe, gynaecologists as breast cancer specialists in Germany and, until recently, in Italy you didn't even need any internal medicine training to become a medical oncologist.

"I've been involved also with the European Society of Breast Cancer Specialists [EUSOMA] on a survey of medical oncology training, which shows a pretty disastrous level of difference; we proposed a template of skills, but take up has been very poor."

Meanwhile in Milan it did not take long for Di Leo to become frustrated with patients' unmet needs, such as pain and lack of choice of drugs to control disease. "I started with prostate cancer, where the drugs we had were mostly not helpful for some patients because we had not yet made much progress in making the links between biology and the clinic, such as how to tackle hormone-refractory prostate cancer, which was the first trial I was involved with. The labs may have been making exciting discoveries but we were not translating them into clinical practice, so much of my research then was disappointing."

In Milan at that time Di Leo did not have the opportunity to step up to help close this major research gap, and he applied to several centres abroad, preferring to remain in Europe rather than go to the US, where he had already completed two short spells as a visiting physician. He succeeded in landing a full-time post in the chemotherapy unit at the Jules Bordet Institute in Brussels. "The institute certainly wasn't the force it is now back in 1996," he says, "but Martine Piccart was there and just starting on her major work in breast cancer, and as soon as I met her, any doubt I had disappeared."

Piccart-Gebhart, as she is now, had just started the Breast International Group (BIG), and she immediately pitched Di Leo into international collaborative research and also supplied that vital lab-clinic interaction he'd been missing in Milan. "I found that research doesn't have any borders and that you can collaborate with the best people by finding who is working on complementary aspects of a problem elsewhere. It opened a new world to me."

Di Leo was given one of the first personalisation research projects in breast cancer, comparing an anthracycline drug with the CMF regime in early-stage disease to see who would benefit most from which treatment. "We collected tissue from centres around Belgium, which was successful as it is not a large country and people were very helpful, and we focused on the topoisomerase II alpha [topoIIα] marker, finding also a group in Finland that was expert in the lab work, while we had the clinical side. We invited them to a seminar in Brussels – I remember how excited everyone was that an enzyme in the nucleus of a cancer cell could be helpful at predicting the outcome of a treatment.

"The hypothesis was that the amplification of the topoIIα gene was associated with the activity of the anthracycline drug – if there was protein overexpression then the drug would hit its target and be particularly effective, and our results were positive and confirmed by other groups. But when I look back on our 2002 paper, I now see that the problem turned out to be more complex, and this has not led to a conclusive change in practice – it needs to be combined with other biological information. But what it did lead to was a new field of research, which is targeted chemotherapy." The search is on now for more

"I found research doesn't have any borders and that you can collaborate with the best people elsewhere"

biomarkers that could potentially be helpful in selecting tumours that are particularly sensitive to DNA damaging cytotoxics.

Di Leo went on to run one of the first BIG trials, on the taxane docetaxel, and its role in breast cancer, identifying centres worldwide and recruiting people to conduct the research. "I also helped set up a translational research unit with pathologist Denis Larsimont, to go back to the tumours and see what benefit we were gaining – it was what I wanted to do in Milan but only achieved it in Brussels. Martine Piccart helped drive funding for the lab, and it grew rapidly, and it was hard to leave it when I came to Prato. But it's been a model for what I've gone on to do here."

Following his move to Prato in 2003, Di Leo has considerably upped his involvement in international research and conferences, finding himself much in demand as he continues to research the targeting and optimal use of systemic therapies, together with his team and colleagues abroad. They are also pursuing more fundamental laboratory science such as studying the characteristics of circulating tumour cells.

Di Leo recently presented research about optimal dosages for fulvestrant. "The hormonal therapy agents are for the 60%–65% of women with endocrine disease, but within this group there are half who are very sensitive and half less so. Most don't need chemotherapy and it has been the first generation of genomic signatures that has helped consolidate this concept."

The MINDACT trial, the large project that is using a genomic signature that could better determine which women can avoid chemotherapy, is a good study, he comments. "It's logistically complex but has been the first attempt to test such personalisation on a large scale – other trials are mainly retrospective and of moderate size. It's not going to provide all the answers but there have been some big surprises – the signature has shown the exact opposite in some cases of what you would expect when you were convinced to give or not give chemotherapy based on traditional markers, and the grey area we are considering here is not small – it is 25%–30% of the endocrine-sensitive population."

New chemotherapy agents, he adds, are also now available that are helping to improve quality of life, for instance because they can be taken orally. "You can see how it lifts women's spirits when you offer them less intensive treatment," he says.

Then there are of course the targeted biological therapies. "While some have clearly changed the story of a disease – trastuzumab and lapatinib for HER2-positive breast cancer, and imatinib for CML and GIST – the new wave of drugs has not given us what we expected. I'm not saying they are not good – they work, but the benefit is not great and some are associated with relevant side-effects. What we need to do is carry out much more work on trials on who will derive the most benefit from these drugs and stop trialling targeted treatments on untargeted populations." The classic examples, he notes, are the anti-EGFR therapies, which were only marginally useful in tumours such as lung overall, but have since been found to be active in certain groups.

But faced with the Catch 22 of not knowing whom to target until the expensive large trials have been done, Di Leo reckons that much gain could be made by much closer interaction with laboratory scientists. "The problem is clinicians and pharmaceutical companies don't talk to them enough – for example, with agents such as the anti-angiogenic

"We need to stop trialling targeted treatments on untargeted populations"

A constructive partnership. Di Leo's wife, Laura Biganzoli, is a medical oncologist running the geriatric oncology programme at the same hospital

drugs, the lesson they have given us is to use lower doses continually. Instead we were giving higher dosages for a shorter time."

He also reckons that the new levels of complexity under investigation about intra-patient heterogeneity – that is, variation in a tumour within an individual – will provide vital clues to progressing the targeting story. Following the classification of breast cancer into its main molecular types – luminal A and B, HER2 and basal (triple node negative) – the next steps are to look at how the different types of cell that make up these tumours behave and interact with the host, among other factors.

Not all cancers of the HER2 type, for instance, behave in the same way, he points out, and there is crossover between the groups; the second generation of genomic signatures is attempting to provide information across the subgroups. "Evidence is emerging that exciting new agents such as the PARP inhibitors – which could be most active in the hard-to-treat triple-node-negative cancers that often affect younger women – might also be active in other subtypes of breast cancer." The PARP inhibitors – which indeed have generated much interest in the cancer community – could be teamed with cytotoxic drugs to make a double attack on the DNA repair mechanisms in tumours, he adds.

With some parts of a tumour interacting with the host in different ways, or an agent suppressing one region and not another, and the heterogeneity among the first level of subtypes, Di Leo says what we need is a 'geography' of each breast cancer. Much of the latest thinking was discussed at IMPAKT, a European translational research meeting in Brussels in May, that Di Leo co-chaired with Christos Sotiriou (a former colleague at the Jules Bordet), and which is now in its second year. "It fills one of the main gaps in European breast cancer meetings, although I would still like to see more smaller events for young investigators and clinicians." (Webcasts of IMPAKT talks can be replayed at esmo.onsite.tv/impakt2010, including one on metabolomics by Catherine Oakman, an Australian oncologist working at Prato and one of Di Leo's current key co-authors. The metabolomics work is being done in conjunction with the Memorial Sloan-Kettering Cancer Center in New York.)

"Given the biological heterogeneity within the same tumour, we may need a 'map' of each breast cancer"

Another important part of the picture he mentions is molecular imaging. "With the new tracers we have now we can see the tumour's metabolic activity, and if it's dying, growing or invading. For example, BIG is looking to start a neoadjuvant study using latest imaging techniques for an important target for oestrogen-positive tumours."

Meanwhile, in the clinics at Prato, the number of new cancer cases seen has shot up to 1500 a year and Di Leo's team is monitoring some 20,000 patients within the regional network structure. "Italy has decided to invest in regional development, and each region is reorganising its health services to provide better care and prevent patients moving between areas, which would reflect badly on our care and also be a loss of funds," he says. Competing to offer the best care can only be good, he adds, so long as protection is provided for regions in the south of Italy that historically have been less competitive.

Just as a cancer treatment decision is often the only opportunity, so too is the first meeting with a cancer patient. "We schedule at least 45 minutes for a first consultation – if a patient feels they are welcome and their problem is well understood, they are much more likely to trust us if we need to help them with more bad news, or if we need to change their treatment.

"What we also do – which is also very demanding in time – is have a day each week when patients and their families can come in and talk to us about their situation, and where we do not schedule any clinical activities. We discuss concerns about treatment, clarify issues and get feedback about how we are doing, which we also do with questionnaires. You can get so wrapped up in treatment plans that you may not discover, as we did, that actually some patients are most concerned about not being able to park by the clinic when they came for chemotherapy."

For their part, he promotes among his clinicians not only good communications but also consistent practice according to guidelines. As he notes, with many expensive drugs at their disposal, the only way to control costs at local level is to give them correctly – not over- or underused. "We have weekly meetings where we discuss who should have treatments and who should not. I'm trying to keep a high level of consistency – it would not be good if one oncologist was denying a drug but next door another was giving it to the same patient."

Among his many activities Di Leo sits on the St Gallen panel – the treatment consensus conference on breast cancer held every two years in Switzerland – but he warns about the use of guidance and tools that do not provide an indication of individual benefit. He has a particular concern about oncologists who rely overly on Adjuvant! Online, the web-based resource. "It's easy to use and you get nice graphs of risks and benefit but it can mislead about the

SAY GOODBYE TO UNTARGETED TRIALS

The hugely complex nature of breast cancers – their heterogeneity – poses major challenges for oncologists making decisions about chemotherapy because the results from trials are often hard to tailor for an individual patient. As Di Leo and colleagues explore in a review paper, 'Adjuvant chemotherapy – the dark side of clinical trials. Have we learnt more?' (*The Breast* 18 S3), there is heterogeneity not only in the biology of breast cancers, but also in treatments according to dose and scheduling, in mechanism of action (some drugs have non-cytotoxic benefits, for example), and in risk – some women do well even without adjuvant treatment that many would have given.

The paper gives a good overview of progress and promise in establishing markers to unpick some of this variation and target cytotoxic treatments better. And the message is clear – this is not the future but should be the focus of current work. A recent editorial written by Di Leo and Oakman titled 'Ode to a past emperor' (*JCO* 28:18) is a devastating critique of a cytotoxic chemotherapy trial reported in the same issue where they take apart its claim for significance, pointing to poor design and missed opportunities to investigate beyond the 'one size fits all' mentality. As they say, "Whereas the old generation of clinical trials has been pivotal in shaping our adjuvant chemotherapy approach, the rule of the old empire has come to a close… Patient eligibility was defined by tumor risk factors. Future generations of trials must abandon this method of patient selection and define eligibility by tumor biology… The era of breast cancer as a homogenous disease is no more."

benefits of hormonal and chemotherapy as it assumes all patients derive equal benefit. It should not be used for treatment decisions, but it can be useful for estimating prognosis, say the 10-year risk of death of someone with a small, node-negative, endocrine-resistant tumour."

Along with BIG, other major groups that Di Leo and Prato work with include the International Breast Cancer Study Group (IBCSG), and the Oxford-based Early Breast Cancer Trialists' Collaborative Group, which crunches data from trials worldwide to understand better what is happening with systemic therapies. Major problems persist, however, in the design and aim of many trials, he says. "We are in a changing phase. Typical examples are the taxane trials of the last decade, some of which have not yet reported. We have some 60,000 patients in these trials – far too many and we are duplicating effort in too many studies. In some cases investigators prefer to be leaders of a small trial – we simply do not need 25 or more trials to demonstrate the effectiveness of taxanes. What's more, many of these trials cover all patient types but on their own are not big enough to reveal any significant data about subgroups."

Di Leo has also been one of the few Europeans on an important committee at the American Society of Clinical Oncology (ASCO). "This was on grant selection for young investigators. I'm very keen to promote younger people and I send them to conferences where I can, although the organisers obviously want the senior people to come. I also give them first authorship on papers. I think if you are working at a centre where you cannot research a new drug or marker, you can instead discover promising young people as an equally important contribution." As Di Leo himself is only 46, this is a mark of his own considerable achievement in the first half of his career.

Di Leo is now on the scientific advisory boards of Susan G Komen for the Cure and the Breast Cancer Research Foundation, both of which allocate many millions of dollars of research funds a year, with Prato among the beneficiaries. Di Leo recognises that sometimes advocacy groups do not push in a logical scientific direction. "But overall the balance is positive – before these groups came along many issues simply were not in the minds of clinicians, such as all those personal variables for treating someone with advanced cancer. And they are on a learning curve too – for example, when I gave a talk to a Europa Donna meeting at the European Breast Cancer Conference in Barcelona on targeted chemotherapy, I found they had a level of caution that was not apparent 10 years ago."

One major factor in his life that spans both home and work is his wife, Laura Biganzoli, who is a medical oncology specialist based in his own department, and whom he met in Milan. "Yes, I'm nominally her boss, but she runs her own programmes in the important and emerging field of geriatric oncology. The good side is that I have someone I can trust and talk to about work, but the bad side is you can talk too much about it back at home. But the key point for anyone who follows my type of career is to have an understanding and supportive family, especially given the travelling and late working I have to do." They have a daughter, Federica, who was born in Belgium – Di Leo keeps telling her she's part of the new Euro generation when she's teased at school about not being a proper Italian.

Among his key mentors and colleagues are of course Martine Piccart-Gebhart, and also Aron Goldhirsch at the European Institute of Oncology in Milan, who pioneered understanding of the complex biology behind endocrine treatment in breast cancer.

Plans for the next few years are clear. "I'm continuing to push the research on personalising chemotherapy – it will be part of our treatment options for a long time to come. I want also to accelerate and improve the efficiency of trials in BIG and IBCSG. And here in Prato I'll continue to improve care, ensure long-term commitment to oncology, and make us more visible in the wider cancer community, especially by promoting young people to take leadership positions in the clinic and lab."

Those who had not heard of Prato now have a new beacon to add to the cancer map.

He has a particular concern about oncologists who rely overly on Adjuvant! Online, the web-based resource

Neurological side-effects caused by recently approved chemotherapy drugs

Many recently approved anti-cancer drugs have neurotoxic side-effects, which in some cases limit the dose levels patients can receive. Oncology teams need to know how to check for warning signs and symptoms and how to manage these toxicities to ensure patients receive the optimal therapeutic treatment while minimising severe or chronic side-effects.

Oncologists know only too well that neurotoxicity represents the dose-limiting toxicity for many of the chemotherapy drugs that we have used for decades. This includes drugs such as the vinca alkaloids, cisplatin and paclitaxel, among others. Neurotoxicity is also important with some of our newer chemotherapy drugs, including drugs that are based on older drugs, such as new formulations of paclitaxel (nab-paclitaxel), nucleoside analogues; new alkylating agents such as temozolomide, and new classes of drugs, including proteasome inhibitors and tyrosine kinase inhibitors.

Focusing on cancer drugs approved since 1999, the classes of drug we will discuss include:

- microtubule inhibitors
- DNA-damaging drugs, such as alkylators and platinating drugs
- nucleoside analogues
- proteasome inhibitors
- immunomodulatory drugs (IMiDs)
- angiogenesis inhibitors.

European School of Oncology
e-grandround

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

In this issue, David Schiff, co-director of the Neuro-Oncology Center, University of Virginia Health System, Charlottesville, USA, reviews the neurological side-effects associated with some of the more recently approved chemotherapy drugs. The material is based on a review co-authored by Patrick Wen and Martin van den Bent (*Nature Rev Clin Oncology* 6:596–603). Andreas Hottinger, from Geneva University Hospital, Switzerland, hosted a Q&A session during the e-grandround live presentation. The presentation is summarised by Susan Mayor.

The recorded version of this and other e-grandrounds, together with 15 minutes of discussion, is available at www.e-eso.net/home.do

NEW MICROTUBULE INHIBITORS

Microtubule inhibitors that have been approved in the last 10 years include nanoparticle albumin-bound paclitaxel (nab-paclitaxel) and ixabepilone.

The well-known peripheral neurotoxicity related to paclitaxel is a sensory neuropathy, which tends to be distal and length-dependent in terms of symptomatology. It is thought to be related to microtubule inhibition of axonal transport, which explains why the longest peripheral nerves – to the feet and hand – tend to be affected first.

Paclitaxel itself is a hydrophobic agent and has to be solubilised in a castor oil or Cremophor (polyethoxylated castor oil) vehicle. Because of the risk of allergic reaction, this requires patients to be premedicated with corticosteroids and antihistamines, and administration requires special intravenous tubing. It has long been thought that the Cremophor vehicle itself may be neurotoxic and it has been hypothesised to exacerbate paclitaxel neuropathy.

Nab-paclitaxel

Albumin-bound paclitaxel takes advantage of the fact that albumin is a natural carrier of hydrophobic molecules. This formulation has paclitaxel in the core, surrounded by albumin on the outside. Albumin binds to its natural receptor, the gp60 receptor, and gp60-caveolin binding delivers the drug in transcytotic vesicles across the endothelium to the tumour.

Nanoparticle albumin-bound paclitaxel has a favourable toxicity profile and patients don't require premedication with corticosteroids. The drug can be administered rapidly, which is convenient for patients and centres providing their treatment. The drug has activity in some patients who have breast cancer that is refractory to standard taxanes. As such, the drug has been approved in the United States for metastatic breast cancer.

Initial studies suggested that nanoparticle albumin-bound paclitaxel might have less neurotoxicity than paclitaxel. Unfortunately, subsequent studies have not confirmed this. The neuropathy seen with nanoparticle albumin-bound paclitaxel is a purely sensory neuropathy, which, as with standard paclitaxel, increases in frequency with a higher per cycle dose as well as with weekly administration. At standard doses, about 70% of patients have grade 1, very mild peripheral neuropathy, and up to 10% of patients have grade 3 peripheral neuropathy (based on the NCI Common Toxicity Criteria [CTC] scale), which means neurotoxicity that interferes with activity of daily living. Fortunately, peripheral neuropathy tends to improve fairly rapidly by one to two grades over a median of three weeks when the drug is stopped. Most patients can then be restarted on this formulation with a modest dose reduction.

Ixabepilone

Ixabepilone has a distinct structure from paclitaxel, although it has a ring structure that is somewhat similar. It was the first drug in a new class – the epothilones – and is a macrolide antibiotic derived from a myxobacterium. It binds tubulin, in a similar way to all the taxanes, either at, or very near, to the taxane-binding site.

Like the taxanes, ixabepilone enhances microtubule stabilisation or polymerisation. In a similar way to standard paclitaxel, it is formulated in a Cremophor vehicle. It is active in some patients with taxane-resistant tumours. Unlike paclitaxel, it is not a substrate for P-glycoprotein.

As with taxanes, the chief toxicities with ixabepilone are neuropathies and neutropenia. The neuropathy is very similar to that with paclitaxel. At a standard dose of 40 mg/m^2 every three weeks, about 60% of patients have mild grade 1 peripheral neuropathy and 10%–15% of patients have grade 3 peripheral neuropathy. As with taxanes, patients complain of hand and foot paraesthesias, but motor or autonomic involvement is rare.

Neurotoxicity is cumulative, but tends to improve within a month or two after the drug is discontinued or the dose reduced. We have recommended dose modifications for patients with neurotoxicity (see table below). Baseline neuropathy does not appear to be a contraindication for administration of ixabepilone.

DNA-DAMAGING AGENTS

Oxaliplatin

Oxaliplatin is a platinum drug in the same family as cisplatin and carboplatin. It derives its name from the oxalate moiety attached to its ring structure. Unlike the other approved platinum drugs, this forms bulky DNA adducts. Unlike cisplatin, oxaliplatin does not cause ototoxicity (damage to the auditory nerve), but it has some rare neurotoxicities at high cumulative doses, including blurred vision, ptosis (drooping of the upper eyelid), Lhermitte's sign (an electrical sensation that runs down the back and into the limbs),

DOSE REDUCTION FOR NEUROPATHY WITH IXABEPILONE

Grade 2 ≥ 7 days:	reduce dose by 20% to 32 mg/m^2
Grade 3 < 7 days:	reduce dose by 20% to 32 mg/m^2
Grade 3 ≥ 7 days:	discontinue

urinary retention and reversible posterior leukoencephalopathy syndrome (RPLS, which can cause headaches, confusion, seizures and visual loss). Its main neurotoxicity, which is also its dose-limiting toxicity, is peripheral neuropathy. Peripheral neuropathy with oxaliplatin occurs in both chronic and acute forms.

The chronic neurotoxicity or peripheral neuropathy with oxaliplatin is very reminiscent of the peripheral neuropathy that occurs with cisplatin. It is generally a purely sensory syndrome that tends to manifest as distal sensory loss and paraesthesias. Electrophysiological studies of patients show that this is an axonal neuropathy, or perhaps a neuronopathy or ganglionopathy, because oxaliplatin accumulates in the dorsal root ganglia, which does not have the same blood–nerve barrier as the rest of the peripheral nerve.

The incidence and severity of oxaliplatin neurotoxicity is clearly a function of cumulative dose. Patients treated at a dose of around 800 mg/m^2 have a 15% risk of grade 3 peripheral neuropathy. At a higher cumulative dose, approaching 1200 mg/m^2, fifty per cent of patients treated with oxaliplatin have grade 3 peripheral neuropathy. Unfortunately, this often occurs while the patient is still responding clinically to oxaliplatin.

Another problem that we see both with oxaliplatin and cisplatin is 'coasting', in which patients may worsen clinically or even develop neuropathy for the first time a month or two after discontinuing drug treatment. Most patients make at least a partial recovery from oxaliplatin neurotoxicity, but this tends to be slow, taking months (a median of three months) rather than weeks as with taxanes, and recovery is invariably incomplete as much as six to eight months after treatment is complete.

Acute oxaliplatin toxicity

Acute oxaliplatin toxicity is almost ubiquitous and a unique phenomenon. It consists of cold, exacerbated paraesthesias, which typically involve the hands, feet and perioral regions. Patients can also have these paraesthesias or dysaesthesias in the throat, pharynx or larynx. This can be unpleasant and frightening for patients, giving them the feeling that they're having difficulty breathing or swallowing. However, it is not a true anaphylactic reaction. Patients may become hoarse as result of acute toxicity of oxaliplatin. The onset is generally rapid, within hours of infusion of oxaliplatin, and may last a few days.

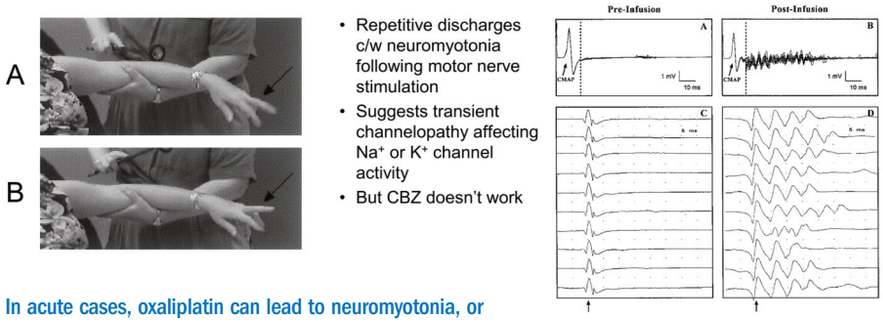
Neuromyotonia is a unique manifestation of acute oxaliplatin neurotoxicity, which results in delayed relaxation. Tapping on the motor branches of the radial nerve – on the posterior interosseous nerve in the forearm – will normally cause a brief contraction lasting up to a few hundred milliseconds. In most patients receiving oxaliplatin there is a sustained contraction lasting several seconds (see figure below).

Repetitive after-discharges are the electrophysiological hallmark of neuromyotonia (see figure). This suggests, as in other causes of myotonia, a transient channelopathy affecting either the sodium or potassium channel. However, carbamazepine, the usual treatment for other causes of neuromyotonia, appears to be ineffective in most patients with oxaliplatin-induced neuromyotonia.

Oxaliplatin peripheral neuropathy – both acute and chronic – represents a clinical problem. The acute neurotoxicity can be managed to some extent by educating patients, so that they're not unduly surprised when they develop symptoms, and they must also be educated to avoid cold exposure. There are some data to indicate that prolonging the infusion of oxaliplatin to decrease the peak dose decreases the risk or intensity of this phenomenon. However, this is not particularly convenient for patients or for infusion centres.

Based on the hypothesis that the oxalate breakdown product of oxaliplatin might chelate calcium and magnesium cations, French investigators did a retrospective cohort study looking at groups pre-treated with calcium and magnesium salts. Results showed that the administration of salts substantially reduced the acute neurotoxicity

DELAYED RELAXATION WITH OXALIPLATIN



In acute cases, oxaliplatin can lead to neuromyotonia, or delayed relaxation, which does not respond to carbamazepine

Source: R Wilson et al. (2002) Acute oxaliplatin-induced peripheral nerve hyperexcitability. *JCO* 20:1767–1774. Reprinted with permission. © 2008 ASCO. All rights reserved

and also decreased the chronic peripheral neuropathy seen with oxaliplatin administration (*Clin Cancer Res* 10:4055–4061).

Based on this observation, two prospective randomised phase III trials were initiated to try to prove this. The first was the CONcePT trial in metastatic colorectal carcinoma. The second was conducted by the Mayo Clinic and the North Central Cancer Treatment Group, using oxaliplatin in the adjuvant setting. Both of these studies randomised patients to calcium and magnesium infusions versus no infusions.

The CONcePT trial was closed early on interim analysis because of a suggestion that tumour response rates were lower in the patients receiving salt infusions. As a result, the North Central trial was closed preliminarily as well. Central review of cases in the CONcePT trial showed that salt infusion did not decrease responsiveness of colorectal carcinoma to oxaliplatin, but, unfortunately, these trials were not reopened.

Data on the effectiveness of salt infusions – in terms of reduction in neuropathy – suggested some benefit. In the CONcePT trial, there was a suggestion of improved patient-recorded outcomes for acute symptoms (*JCO* 26:4010). The North Central trial suggested a decrease in severity and prolonged time to development for chronic peripheral neuropathy (*JCO* 27:15s suppl; abstr 4025). I think it's fair to say the jury is still out, but at the moment it is reasonable to administer these salts prophylactically and there is no evidence that they decrease the effectiveness of oxaliplatin in terms of its chemotherapeutic effect.

Temozolomide

Temozolomide is the neuro-oncologist's favourite drug! It is an oral methylating agent, structurally related to dacarbazine. It achieves very good blood–brain barrier penetration, making it useful in gliomas. Its principal cytotoxic effect seems to be a methylation of the O6 position of guanine in DNA. This O6 methylation is a lesion that is repaired by the DNA repair protein methyl guanine methyl transferase (MGMT).

When temozolomide is administered as a single agent, there is no clearly defined neurotoxicity. However, there is some neurotoxicity when it is combined with radiation therapy for newly diagnosed glioblastoma. The clinical benefit of temozolomide seems chiefly to be in patients who are deficient in MGMT, which fits with our understanding of how it works.

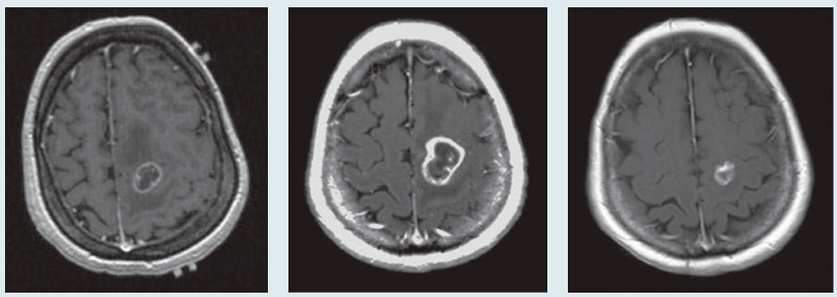
Pseudoprogression

The clinical syndrome of pseudoprogression has been well recognised for decades. Patients treated with radiation therapy for high-grade gliomas sometimes show apparent worsening on a CAT scan or MRI, with an increase in contrast enhancement and increased vasogenic oedema, usually developing several weeks after the completion of fractionated radiotherapy. This is typically a transient phenomenon.

With radiation therapy alone, the literature suggests that pseudoprogession occurs in about 10% of patients treated with usual doses of radiation (up to 60 Gy) for high-grade glioma. Since we've been using temozolomide combined with radiation, we've seen it more frequently, in perhaps 20%–30% of patients.

Looking for a biomarker for pseudoprogression, Brandes and colleagues conducted a study in which just over 100 patients newly diagnosed with glioblastoma were treated with radiation and temozolomide. They were scanned at the conclusion of radiation therapy and half (50) showed a worse-looking MRI scan, while 53 patients had a stable or improved tumour.

A case of pseudoprogression with temozolomide



Pre-RT/TMZ | 1 month post treatment | 1 year post diagnosis

This series of MR scans comes from a woman in her sixties who had a left posterior frontal glioblastoma. The first scan is before radiation therapy. She was then treated with standard radiation and temozolomide. One month after her radiotherapy, her lesion had essentially doubled in diameter, with more vasogenic oedema. We were hopeful that this represented pseudoprogression, so we sat tight and continued her temozolomide. Subsequent scans improved and her one-year scan showed considerable improvement. She is now three years from completion of radiation and remains without evidence of recurrent tumour. In hindsight, this was clearly a case of pseudoprogression.

Regardless of how their MRI looked, the patients were continued on temozolomide and rescanned three months later. About two-thirds of patients whose scans immediately after treatment looked worse, but looked stable or better by this time, were deemed to have had pseudoprogression. Those whose scans looked worse after treatment, and continued to show no improvement, were considered to be resistant to temozolomide treatment and have progressive disease.

Looking at the MGMT status of the patients' tumours (based on promoter methylation) the majority of those with pseudoprogression had MGMT promoter methylation. In the patients who had temozolomide resistance and true tumour progression shortly after completing radiation therapy, the overwhelming majority had unmethylated MGMT promoter analysis (*JCO* 26: 2192–2197). If confirmed in further studies, the MGMT promoter methylation status will help us decide whether a patient is likely to have pseudoprogression or true tumour progression shortly following the conclusion of radiation therapy.

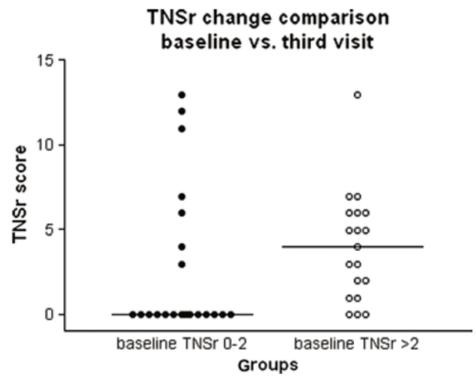
NUCLEOSIDE ANALOGUES

Nucleoside analogues are mostly used to treat haematologic malignancies. Nelarabine is a recently approved Ara-G prodrug that is used to treat patients with T-cell haematologic malignancies. It achieves very good penetration of the blood–brain barrier and has activity in leptomeningeal T-cell malignancies.

Neurotoxicity is very common with nelarabine, affecting around 40% of patients, with about half suffering severe neurotoxicity (of the order of grade 3). This neurotoxicity comes in two different forms: sensorimotor peripheral neuropathy and headache, encephalopathy and seizures.

Clofarabine is a deoxyadenosine analogue that does not cross the blood–brain barrier very well, and is only occasionally associated with mild headache. Cytarabine has been used intrathecally for many years, but a liposomal formulation has been approved more recently. The liposomal formulation almost invariably causes arachnoiditis, manifesting as headache, meningismus and aseptic meningitis-type symptoms. As a result, patients are routinely given prophylactic treatment with dexamethasone (4 mg twice daily). Despite this, mild arachnoiditis-type symptoms are very common. One report, from the group at MD Anderson, suggests that liposomal cytarabine may synergise with either high-dose intravenous methotrexate or cytarabine and predispose patients to neurotoxicity in the form of encephalopathy or corda equina syndrome. This observation requires confirmation.

PERIPHERAL NEUROPATHY AFTER BORTEZOMIB



Painful neuropathy in the hands and feet is a dose-limiting side-effect of bortezomib; the graph shows that it is much more common in patients who had a total neuropathy–reduced (TNSr) score of more than 2 before treatment

Source: F Lanzani et al. (2009) Role of a pre-existing neuropathy on the course of bortezomib-induced peripheral neurotoxicity. *J Peripheral Nerv Syst* 13:267–274 Reprinted with permission. John Wiley and Sons

PROTEASOME INHIBITORS

Bortezomib

Bortezomib is the first proteasome inhibitor approved for use in cancer, and is used to treat multiple myeloma and mantle-cell lymphoma. It is also under study in a number of solid tumour malignancies, including non-small-cell lung cancer and glioblastoma.

Neuropathy represents the dose-limiting toxicity of bortezomib. The mechanism is uncertain but the proteasome is believed to be involved in the degradation of ubiquinated proteins, such as NF-kappaB and cyclins, which help push cells through the cell cycle and are important in haematological cancers. Bortezomib causes peripheral neuropathy by targeting the dorsal root ganglia, where there is no blood–peripheral nerve barrier. Neuropathologically, patients who have had nerve biopsies have shown accumulation of ubiquinated cytoplasmic aggregates.

Bortezomib peripheral neuropathy affects the majority of patients, with 64% having peripheral neuropathy of at least grade 1 severity, but grade 3 neuropathy is relatively uncommon, with a rate of 3%. The neuropathy is almost always purely sensory and tends to affect small fibres. It can be quite painful, with burning paraesthesias and dysaesthesias in the hands and feet. However, neurological examination is usually normal.

Bortezomib neuropathy tends to be cumulative and typically appears around cycle 5, which is about 12 weeks into treatment. It is generally reversible on stopping the drug or reducing the dose. A study

showed that patients with peripheral neuropathy before bortezomib treatment were more likely to develop further neuropathy on treatment than those with lower total neuropathy score (TNS) at baseline (*JPNS* 13:267–274) (see figure, p17).

Immunomodulatory drugs

Thalidomide

Thalidomide is a major agent used to treat both newly diagnosed and recurrent multiple myeloma. It was developed as a sedative about 50 years ago, and its principal acute neurotoxicity is somnolence, which occurs in about 75% of patients. To reduce the problem, thalidomide is given at bedtime, starting with low doses. Tachyphylaxis is common, so most patients habituate to the sedative effect.

However, thalidomide also causes a clinically significant peripheral neuropathy. This tends to have strong sensory and autonomic components, but rarely a motor component. The autonomic component manifests most typically as constipation, which affects the majority of patients. The sensory component appears initially as paraesthesias in the hands and feet. On examining these patients, you will find a distal sensory loss to light touch and pinprick with vibratory sense and deep tendon reflexes somewhat spared.

Thalidomide neuropathy is occasionally painful, although this is not usually a prominent part of the clinical picture. It is an axonal neuropathy. As with the platinum drugs, thalidomide neuropathy can worsen during the first few months after discontinuing the drug and recovery is usually slow and incomplete.

Risk factors for thalidomide neuropathy are debated. Some studies suggest that the daily dose is important, while others argue that it is the cumulative dose. Obviously, cumulative dose is related to daily dose, and it appears that a lifetime cumulative dose greater than 20 g can increase the risk of thalidomide neuropathy. Gabapentin is sometimes helpful, as the paraesthesias are unpleasant for the patient, but there are no drugs that reverse the peripheral neuropathy.

The usual recommendation for thalidomide neuropathy is to discontinue the drug. If the patient's condition is worsening and there is no other alternative, we put thalidomide treatment on hold until the neuropathy has improved and then restart at a much lower dose. As both thalidomide and bortezomib are active against multiple myeloma, this combination is under study. However, reports suggest an increased risk of peripheral neuropathy.

Lenalidomide

Lenalidomide is another immunomodulatory drug approved for the treatment of multiple myeloma and myelodysplastic syndrome. It tends to cause much more myelosuppression than thalidomide, but less central and peripheral neurotoxicity. Neuropathy is rare and mild even at high doses. Fatigue and somnolence are also rare. Occasionally, patients have non-specific symptoms such as dizziness or tremor.

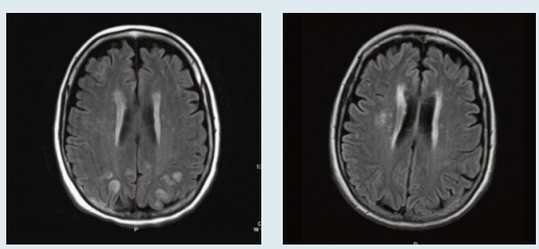
Antiangiogenic agents

Reversible posterior leukoencephalopathy syndrome (RPLS) has been reported with all of the new angiogenesis inhibitors that target vascular endothelial growth factor (VEGF) and its receptor. This syndrome manifests as encephalopathy, seizures, cortical blindness, headache and, generally, very elevated blood pressure. It occurs not only with chemotherapeutic drugs but also with immunosuppressive drugs such as cyclosporine, and in patients with eclampsia and dialysis patients with renal failure.

The pathogenesis remains unclear, but seems to be either a failure of cerebral vasomotor autoregulation or some kind of toxic endothelial injury. This syndrome has been reported both with anti-VEGF agents and VEGF receptor tyrosine kinase inhibitors including sorafenib and sunitinib.

Intracerebral bleeding has been a concern with all anti-angiogenesis inhibitors, including bevacizumab and VEGF tyrosine kinase inhibitors in patients with brain metastases and with bevacizumab in glioblastoma. Use of bevacizumab has long been considered a 'no-no' in patients with brain metastases, since 1997,

A case of reversible posterior leukoencephalopathy syndrome



These MRI scans are of a woman in her sixties with melanoma metastatic to lymph nodes, but not the brain, who was being treated with bevacizumab plus temsirolimus in a clinical trial. She developed a blood pressure of 170/110 mmHg and severe headaches. Her MRI (*left*) showed T2 and FLAIR-hyperintense lesions in the posterior cerebral hemispheres, as well as in the posterior fossa (not shown on the scan). Her hypertension was treated aggressively and bevacizumab was discontinued. A follow-up MRI three weeks later (*right*) showed substantial improvement.

when a patient with hepatocellular carcinoma and an unrecognised brain metastasis in one of the early studies developed an intracranial haemorrhage. This is not withstanding the fact that patients with hepatocellular carcinomas often have coagulopathies and haemorrhagic metastases.

Earlier this year, researchers using Genentech databases published retrospective data looking at the safety of bevacizumab in patients with brain metastases. In the first part of this study, including more than 8000 patients treated with chemotherapy plus or minus bevacizumab, about 100 patients in each of those arms turned out to have brain metastases. Results did not show an elevated rate of intracranial haemorrhage in patients treated with bevacizumab, which is a somewhat reassuring finding.

The study also included more than 4000 patients who had been treated with bevacizumab and then developed brain metastases while on the drug, in open-label, single-arm studies. More than 300 patients developed brain metastases and fewer than 1% of these developed intratumoural haemorrhage (*Clin Cancer Res* 16: 269–278). The researchers concluded that there did not appear to be a disproportionate risk with the use of bevacizumab in the treatment of brain metastases and recommended that we consider not excluding patients with brain metastases from treatment with bevacizumab.

A further prospective study looking at this issue, the PASSPORT study, included more than 100 patients with non-squamous non-small-cell lung cancer and brain metastases. Their brain metastases were resected or irradiated with standard radiation or radiosurgery. They were then treated with whatever standard chemotherapy their oncologist wanted to administer plus bevacizumab.

Patients were followed with brain CT scans or MRI scans at regular intervals, with the endpoint being grade 2 or higher CNS haemorrhage. They were allowed to receive anticoagulants, which were given to almost one-fifth of the patients. No cases of intracranial haemorrhage of any grade were seen, which again supports the idea that bevacizumab can be safely used in patients with treated brain metastases (*JCO* 27:5255–5261).

VEGF RECEPTOR TYROSINE KINASE INHIBITORS

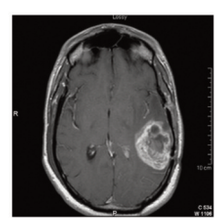
There have been anecdotal reports of intracranial haemorrhage with sunitinib and sorafenib. However, these drugs are widely used for renal cell carcinoma, which is a tumour with a predisposition to haemorrhage – particularly in the brain – even without any specific treatment.

The results of two large, expanded-access open-label studies have been published in the last few months. In the first – a study of more than 300 patients with brain metastases from renal cell carcinoma, who were treated with sunitinib – only one patient had a low-grade intracranial haemorrhage (*Lancet Oncol* 10:757–764). In the second – which included 70 patients with brain metastases from renal cell carcinoma, treated with sorafenib – no intracranial haemorrhages occurred (*Cancer* 116:1272–1280). The authors of both of these reports concluded that the tyrosine kinase inhibitors appeared to be reasonably safe in patients with treated brain metastases.

The oncologic community is well aware that bevacizumab is a useful agent in recurrent glioblastoma. The figure below shows MR scans from a patient with recurrent glioblastoma before and after bevacizumab who was in a trial that led to approval by the FDA. There has long been concern about using bevacizumab for glioblastoma because of the fact that glioblastomas occasionally haemorrhage even without bevacizumab, and the brain is obviously a bad place for an intratumoural haemorrhage.

GLIOBLASTOMA BEFORE AND AFTER BEVACIZUMAB

- GBMs occasionally haemorrhage
  - 1/21 HGG pts receiving bevacizumab had fatal bleed
- Friedman et al. (*JCO* 2009): 167 recurrent GBM
  - 3 gr 1, 1 gr 2, 1 gr 4 haemorrhage
- Kreisl et al. (*JCO* 2009): 0 haemorrhages/48 GBM pts
  - Friedman allowed LMWH, Kreisl didn't
- 21 pts bevacizumab + anticoagulant at UCLA (*Neuro Oncol* 2008)
  - 2 asymptomatic, 1 mildly symptomatic bleeds
  - Risk of bleeding with anticoagulant acceptable



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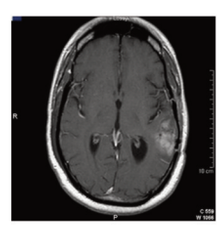


Jan 4 2007

These scans were part of the pivotal study that led to FDA approval of bevacizumab in recurrent glioblastoma; a number of small studies suggest that the risk of intracranial haemorrhage in this setting is 'acceptable'

GBM – glioblastoma multiforme, HGG – high-grade glioma, LMWH – low molecular weight heparin, *Source:* Scans courtesy of David Schiff

In a small study on the use of bevacizumab in recurrent high-grade glioma, 1 in 21 patients had a fatal intracranial haemorrhage (unpublished). A larger study of 167 patients with recurrent glioblastoma multiforme treated with bevacizumab, and allowed to receive anticoagulants if they had venous thromboembolism, found that only five patients had intracranial haemorrhage, and these were mostly of low grade (*JCO* 27:4733–4740).

Similarly, in the report from Howard Fine's group at the National Cancer Institute, none of the patients treated with bevacizumab developed haemorrhages (*JCO* 27:740–745). As such, it appears that the risk of intratumoural haemorrhage with bevacizumab in recurrent glioblastoma – although still not clearly defined – is acceptably low.

The issue of whether patients who are receiving bevacizumab and are on anticoagulants can be safely treated in view of the risk of haemorrhage was looked into by Tim Cloughesy's group at UCLA. They reported 21 patients who were anticoagulated for venous thromboembolism while receiving bevacizumab. There were two asymptomatic and one mildly symptomatic haemorrhages (*Neuro Oncol* 10:355–360).

Overall, the neurological community has accepted a small risk of bleeding with anticoagulation and bevacizumab.

Q&A

Andreas Hottinger, from Geneva University Hospital, Geneva, Switzerland, hosted a question and answer session with David Schiff.

Q: *What is the maximum dose of oxaliplatin for the treatment of colorectal cancer that patients can tolerate? Is there a limit, and, if so, how do you work with that?*

A: I generally leave this decision to my medical oncology colleagues who are administering the chemotherapy. I think that, in the absence of clinically significant neuropathy, there is no reason not to keep going as long as the patient is tolerating oxaliplatin. Obviously, it is a difficult decision if the patient has mild to moderate neuropathy, but is still responding to the drug. That is a decision for the oncologists to make.

Q: *What kind of work-up do you recommend for patients who develop neuropathy on treatment?*

A: The first thing is to try to characterise the neuropathy clinically and then to determine whether it fits with the chemotherapy that the patient has been receiving. Most chemotherapy neuropathies have a distal predilection and they tend to be symmetric. Most of the neuropathies I discussed are either purely sensory or more sensory than motor. We try to sort out from the patient's history and examination if their neuropathy fits with that. Electrophysiological testing is needed in only a minority of patients. One of the great uses of EMG and nerve conduction studies is to determine if a neuropathy is axonal or demyelinating. Most of the chemotherapy neuropathies are axonal neuropathies. Obviously, excluding other possible causes of peripheral neuropathy like alcohol use or diabetes is important. The main use of electrophysiology is to help sort out whether patients have an underlying hereditary neuropathy or an acquired demyelinating polyneuropathy that either is mimicking the chemotherapy neuropathy or is predisposing to a more severe chemotherapy neuropathy.

Q: *Once the patient has developed a neuropathy, what kind of supportive measures do you recommend?*

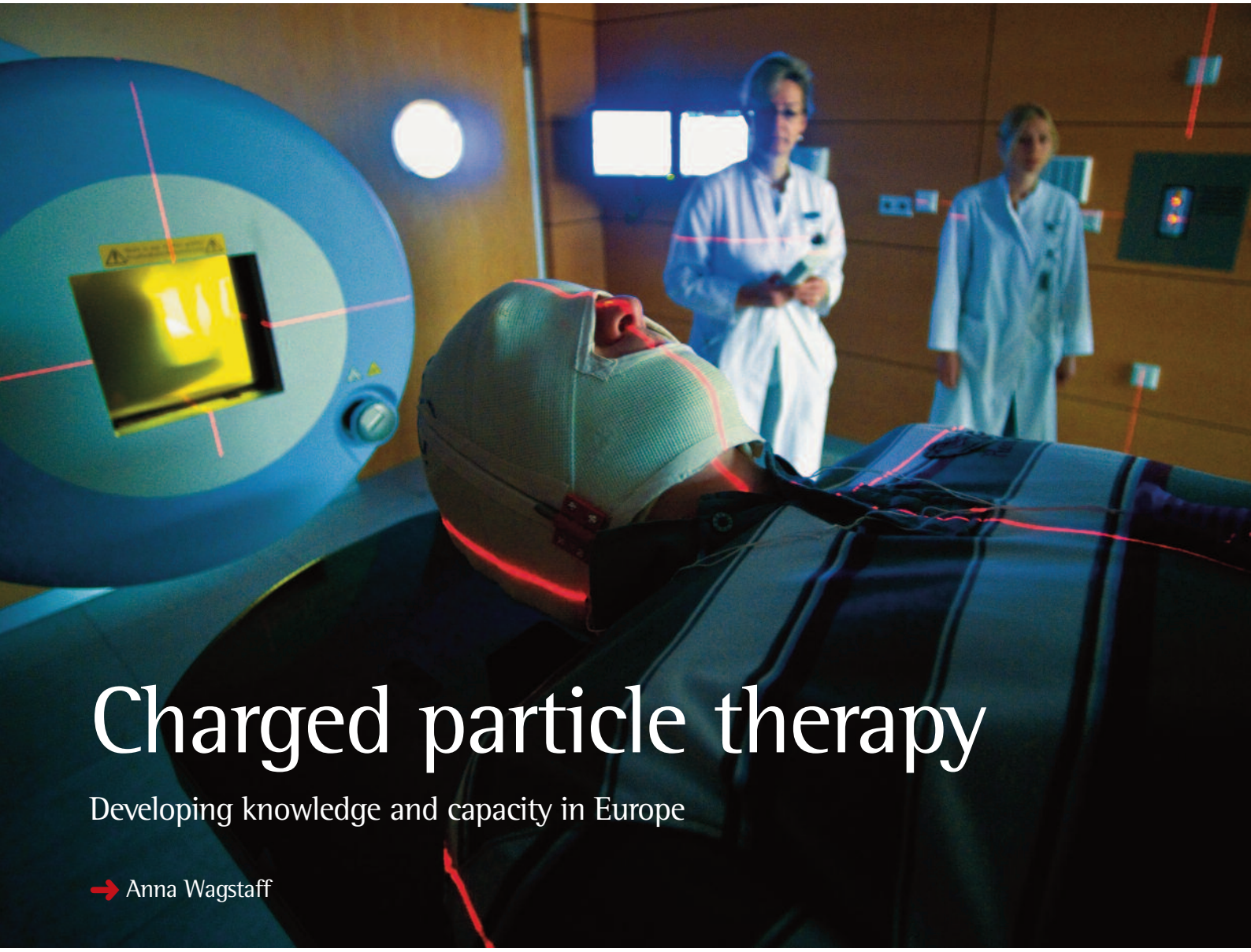
A: We do not have any proven neuroprotective agents, with the possible exception of calcium and magnesium salts with oxaliplatin. Therapy tends to be symptomatic. I don't believe vitamins have been proven to be of much use, except for avoiding nutritional deficiencies in cancer patients that can exacerbate peripheral neuropathy. Treatment is therefore symptomatic with agents such as gabapentin, vigabatrin, amitriptyline and sometimes low-dose opioids for painful neuropathy.

Q: *Why do chemotherapy neuropathies tend to affect sensory neurons over motor neurons, and why do motor neurons appear to be protected from their effects?*

A: The speculation is that the motor neurons are located in the spinal cord, which is protected by the blood–spinal cord barrier. The peripheral nerves may be particularly vulnerable through the dorsal root ganglion, which lies outside the protection of the blood–nervous system barrier.

Q: *What do you suggest for the effective diagnosis of pseudoprogression and its treatment?*

A: We have not found any imaging techniques to be reliably useful. As such, we generally continue temozolomide for at least three months following completion of fractionated radiotherapy, unless the patient has developed disease outside the radiation field.



Charged particle therapy

Developing knowledge and capacity in Europe

Anna Wagstaff

Charged particle therapy has been known for 60 years as an alternative radiotherapy, more precise and potentially more safe and/or effective for some patients. But as Europe grapples with the need for equipment and training, there are calls for caution until more robust clinical evidence has been generated about survival and quality-of-life benefits in the longer term.

Ever since radiation was first applied to treating cancer the challenge has been to maximise the damage to cancerous cells while minimising damage to normal tissue – an equation often referred to as the therapeutic ratio. Killing off healthy cells in the pathway of the beam can do irreversible damage to the heart, lungs or brain, affect the ability to eat, talk or swallow, or breach tissue walls leading to fistulas in the bowel or urinary tract. Low-level damage from radiation raises the risk of secondary tumours in the longer term.

One technique with potential for improving the therapeutic ratio in certain cancers has been known since at least 1946. Charged particle therapy replaces the photon (energy) beam of conventional radiation (X-rays, gamma rays or electrons) by a stream of protons or other sub-atomic particles (collectively known as 'hadrons') or by heavier bodies such as carbon ions.

Unlike photons, which deliver most of their energy and biological impact as they enter through the skin, tailing off gradually as they progress through the body, charged particles release relatively little energy as they enter the skin at high speed. Their greatest impact (known as the Bragg peak) is delivered as they come to rest, after which point they have virtually no impact whatsoever (see figure (a)).

In patients a series of Bragg peaks is needed to hit the tumour over its full depth, and this requirement considerably reduces the advantages it has over conventional therapy with respect to tissue damage on the way in (see figure (b)). However, the potential to protect tissue after passing through the tumour is impressive, and is the main reason why charged particle therapy has so far concentrated on ocular melanoma and tumours at the base of the skull, where avoiding damage behind the tumour is particularly important.

The passage of charged particles seems to create much less disturbance to neighbouring tissue than photons, thereby reducing the low-dose toxicity that is known to increase the risk of secondary tumours. Much of the current interest in this type of therapy centres on its potential to improve outcomes in paediatric patients, for whom late secondary tumours are of particular relevance because they have their whole lives ahead of them.

Interest has also been growing in exploring the distinct radiobiological properties of charged particles, which could help identify the sorts of tumours that might be most appropriate for this type of treatment. The biological impact of charged particles in terms of DNA damage is known to be generally higher for charged particles than photons. Calculated in terms of their relative biological effect (RBE) compared to photons, carbon ions have an RBE of 3–4, while that of protons is around 1.1. This raises the possibility that tumours that respond poorly to conventional radiation may respond better to the heavier biological onslaught of carbon ion therapy. This would be of particular benefit in certain cancers of the salivary gland, sarcomas, bone cancers and pancreatic cancers, among others.

Animal and *in vitro* studies have raised hopes that heavy ion therapy might also suppress angiogenesis and metastasis, which are known to be stimulated by X-rays, although this has yet to be demonstrated in patients.

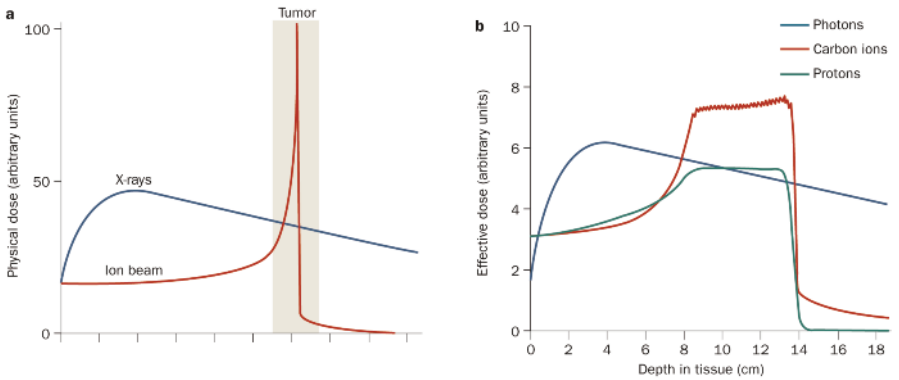
A SLOW START

With all this potential, it might seem strange that charged particle therapy has not developed faster since Robert Wilson published his pioneering paper on The Radiological Use of Fast Protons in the journal *Radiology* back in 1946, or indeed since the first experimental treatments of cancer patients, which were performed in physics research facilities in Berkeley, California (1954) and Uppsala, Sweden (1957).

More than 50 years on, according to the Particle Therapy Cooperative Group, there are still only 20 charged particle facilities currently treating deep tumours (as opposed to surface tumours like ocular melanoma), and only four of these, two in Germany and two in Japan, are using carbon ions.

One problem, undoubtedly, is the size

COMPARISON OF DOSE-TISSUE DEPTH PROFILES



Particle therapy can hit a target more precisely than conventional radiotherapy

Source: M Durante and JS. Loeffler (2010) Charged particles in radiation oncology. *Nature Clin Rev Oncol* 7:37–43. Reprinted by permission from Macmillan Publishers Ltd, 2010

and the cost of the kit. Charged particle therapy is not something a keen group of young post-docs can dabble in. This is particle physics – not quite CERN, perhaps, which is built to accelerate particles to close to the speed of light – but the principles are the same.

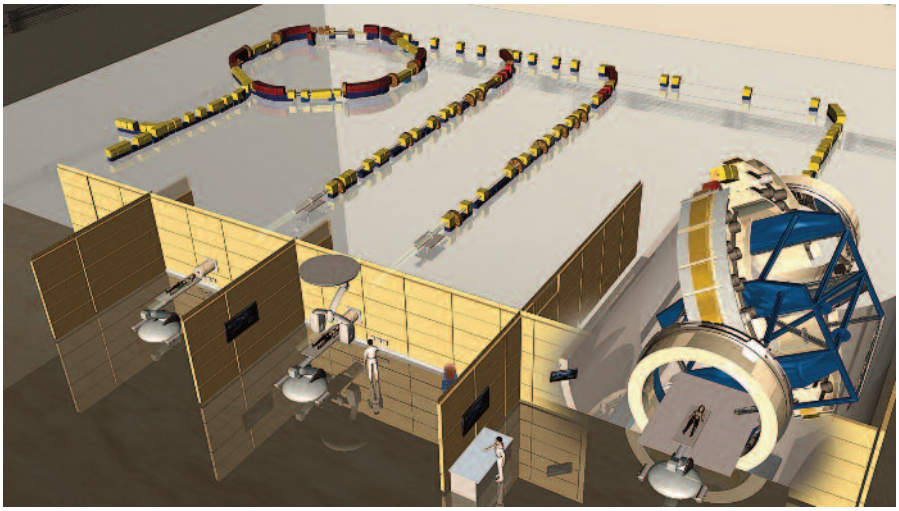
Synchotrons comprise huge circular arrangements of magnets that accelerate the particles, weigh upwards of 100 tonnes and measure around 90 metres in circumference. More advanced facilities also house huge gantries capable of rotating the synchrotron to alter the angle of the beam. Villigen, in Switzerland, and Munich and Heidelberg in Germany, are home to the only European facilities currently using gantries – the buildings that accommodate them have been likened to cathedrals.

The cost of building one of these facilities is estimated at €125 million – rising to €150 million if you want a gantry thrown in. Running costs are also higher, with around twice the level of staff and higher levels of expertise compared with conventional facilities.

In any case, developing the potential of charged particle therapy had to await progress in three-dimensional imaging and computer modelling. Without these, the advantages of the highly concentrated 'Bragg peak' biological impact remained largely theoretical in all but the most shallow tumours, as there was no accurate way to programme the equipment to deliver concentrated damage throughout the tumour tissue, and avoid falling short or, worse, hitting the very organs behind the tumour that charged particle therapy is meant to protect.

Significant improvements in conventional radiotherapy techniques may also have contributed to a lack of urgency in developing charged particle therapy. Conformal techniques, which deliver the full therapeutic radiation dose using multiple low-dose beams that converge on the tumour from many angles, have proved very successful in reducing acute toxicity to healthy tissue, though it is still a little early to draw definitive conclusions about late secondary tumours and survival. The ability to modulate the intensity of the beam according to the density and depth of different parts of the tumour, and the use of powerful software to deliver a finely calibrated treatment plan to a moving tumour (as in the lung) using real-time image guidance, offer further sophistication, while brachytherapy (implanting radioactive pods next to the tumour), is widely used for certain highly localised tumours.

An impressive bit of kit. This schematic representation of the charged particle therapy facilities at Heidelberg University Hospital shows the huge scale of the equipment. The circular arrangement, top left, is the synchotron that accelerates the particles; the large construction at the bottom right of the picture, dwarfing the patient, is the gantry that allows the angle of the beam to be rotated



HEIDELBERG UNIVERSITY HOSPITAL

As a result, in Europe, the task of making progress with charged particle therapy has been left to a small band of dedicated researchers. Among them is Roberto Orecchia, head of the Centro Nazionale di Adroterapia Oncologica (CNAO) in Pavia, Italy, where a new proton therapy facility has recently been completed. The facility is based on a design developed by PIMMS (Proton and Ion Medical Machine Study), a European collaboration involving CERN and charged particle therapy research outfits in Germany, Austria, the Czech Republic and Italy.

That spirit of European scientific collaboration has been a real driving force for Orecchia. In 2002 he helped pull together diverse European efforts in this field through the European Network for LIGht ion Hadron Therapy (ENLIGHT), which links more than 150 clinicians, physicists, biologists and engineers from around 50 European universities and research institutes in 16 countries. "We were a community of scientists who were very interested in developing a new field of research in terms of particle therapy," says Orecchia. "This was not just from a clinical point of view, but to explore the physical and biological characteristics of particles which are very interesting because they can potentially overcome the problem of radioresistance to X-rays. It was also an opportunity to improve the quality of the machine."

Collaboration was strengthened in 2008 with the start of the ULICE programme (Union of Light Ion Centres in Europe). Funded by the EC to the tune of €8 million, it brings together 20 research centres in 11 countries with the aim of

establishing non-competitive European platforms for scientific and clinical research and a coordinated approach to developing the technology, helping countries to set up new facilities and gain experience in this area of therapy. This includes making 691 hours of beam time at the CNAO in Pavia, Italy, and Heidelberg University Hospital in Germany, available to ULICE partner researchers – clinical radiation oncologists as well as biologists and physicists.

Orecchia's own main focus is on developing ways to characterise an individual tumour to exploit the potential of particle therapy to best effect. "Because we have an instrument that is very precise and can be very targeted, the first goal is not only to identify where the target is but also to gather highly detailed information about the tumour biology: cell proliferation, differentiation, quantity of oxygen, a lot of different biological parameters."

These studies should help to identify markers that can guide treatment choice – including which type of radiotherapy to use (conventional, particle, or both), fractionation (how many doses should be administered within what timeframe) and other treatment parameters. "We have to find the molecular basis of a new scheme of fractionation," says Orecchia, who hopes that eventually this could lead to reducing the number of fractions to between one and five sessions, "A big reduction if you consider that when I started in radiotherapy the cycle normally lasted 40 sessions."

Improving the equipment is another area of development. "All the machines in operation now are modelled on equipment designed for physics experiments that has been modified for medical use. One of the ULICE topics is to design a new machine as a concept for medical use." The next generation of magnets he believes could reduce the size of a synchotron by up to 50%. There are also efforts to find alternative methods to accelerate the particles, possibly using a laser beam or dielectric wall accelerator, though these are still at an experimental stage.

With the size of the accelerator reduced, more facilities will be able to afford and accommodate the smaller gantries needed to rotate the beam. Orecchia also hopes that the new generation of particle therapy facilities being developed in Europe will all use active scanning technologies that can modulate the energy of the beam according to the precise shape and characteristics of each part of the tumour.

Robotic patient positioning techniques and image guidance systems for treating moving tumours are also important areas for technological improvement.

Hands-on experience

The clinical and transnational access side of the ULICE programme is coordinated from Heidelberg by Jürgen Debus, head of Radiooncology and Radiation Therapy at the University Hospital who explains, "The idea is that we establish a computer network where everyone can refer potential patients, and a committee decides which patients will be entered into the studies, so we can conduct studies on a pan European level and get a faster recruitment of patients."

Three such studies have already been launched. One compares proton therapy with carbon ion therapy in patients with chordoma. Another is exploring the effectiveness of using carbon ions to treat adenoid cystic carcinoma – a salivary gland cancer that responds poorly to conventional radiotherapy.

A third study is looking at combining conventional and proton therapy for patients with glioblastomas. "Typically 50 Gy, which is a substantial part of the treatment, is delivered in the home institution and delivered to a larger volume, where you suspect there is also microscopic spread," says Debus. "The idea of this study is that these patients are being treated with conventional therapy to large volumes and then there is what we call a 'boost', so if there is macroscopically visible tumour, this area is treated by particle therapy."

Avoiding any break between the photon part of the treatment done at the referring centre and the proton boost will be one of the big challenges for this study. "And in the end the question is: are the results better for this than for treatment with conventional radiotherapy."

The intention, says Debus, is that the patients and their doctors will come to Heidelberg for the 'proton boost'. This supports another aspect of ULICE, which is giving hands-on experience to radiation oncologists from centres that are interested in developing particle therapy, but do not yet have an operational facility. "These people will have the opportunity to get training on the one side and also to bring their patients to the facility, treating them by themselves and then going back home. If they want to start their new facilities, they have already trained personnel and can start right away."

The imperative to invest in highly trained staff to operate this technology is a point strongly emphasised by Debus. "Photons are forgivable with dose

"We have to find the molecular basis of a new scheme of fractionation"

distributions in many situations, they are more robust than for proton dose distributions. So you have to know about the sensitivity of the proton dose distribution and behave accordingly."

The facility at Heidelberg was completed in 2007, but only started treating patients in 2009, concentrating on base of skull tumours, typically tumours which are very close to critical structures such as optic nerve or brain stem. They also treat some patients with 'fixed tumours' of the vertebral column or in the pelvic and sacral area. His facility is now in the process of installing cutting-edge image-guidance equipment that should allow them also to treat patients with certain moving tumours within the next two years.

Looking 10 years ahead, Debus estimates that up to 30% of all radiotherapy treatments in Germany will be done using proton or ion therapy. He hopes that the clinical study platform established by ULICE (the programme comes to an end in 2012) will be able to develop robust, European evidence-based guidelines for which patients need this type of therapy and how to treat them.

Clinical evidence

One person keeping a close eye on this process of building up the clinical evidence for charged particle therapy is Michael Brada, professor of clinical (radiation) oncology at the UK Institute of Cancer Research and a past president (2004–2006) of the European Society for Therapeutic Radiology and Oncology (ESTRO). He caused some ripples with a review article in the *JCO* that he co-authored in 2007, which examined the published clinical evidence for proton therapy and concluded there was none.

A follow-up article by the same authors in *The Cancer Journal* in 2009 presented this stark conclusion: "…despite some tens of thousands of patients treated, the published peer-reviewed literature is devoid of any clinical data demonstrating benefit in terms of survival, tumor control, or toxicity in comparison with best conventional treatment."

The reviews looked at the evidence for chordomas and chondrosarcomas of the skull base, ocular melanomas and prostate cancer – now the main tumour treated by proton therapy in the US. They also looked at 'other tumours' and childhood tumours. The first two really raised eyebrows, because they have become established as heartland 'proton therapy territory' – indeed many facilities treat nothing other than ocular melanomas.

Yet according to Brada et al., the 90% local control rate, 85% cause-specific survival and 90% eye preservation rate are no better than the results achieved by high-precision photon irradiation, at least in small tumours.

Equally, while the results for chondrosarcomas of the skull base may sound impressive at 95% five-year progression-free survival, these tumours, argue the authors, tend to be low-grade indolent tumours often with a long natural history. Results after radical surgery, with or without conventional radiotherapy, show 90%–100% five-year survival, so again no advantage for proton therapy can be shown.

As for chordomas, the 73% five-year disease-free survival figure in a series of 621 patients that gets quoted in various reviews, though undoubtedly impressive, is based on a reporting error of data that were anyway so incomplete they would be unlikely ever to have been accepted by a peer-reviewed journal, says Brada. A closer look at that original study, published in *Strahlentherapie* – not a peer-reviewed journal – reveals that the data show a five-year disease-free survival figure of 64% not 73%, added to which, the number of patients was less than half the quoted number, and more than 40% of these were lost to follow-up.

"It just shows what happens if there is no proper peer review and you don't have any checks in the system, and you have enthusiasts... Everybody believes it and quotes it but actually the results aren't true. Everybody says, 'I want to go and have the treatment at a proton facility.'" Given that proton treatment is expensive, and that the patient may have to bear all costs privately, as well as paying for travel and accommodation, there are huge costs involved in this option, says Brada. "And my take on this is: is the benefit such that you should sell your house to go and have this treatment?"

And so it goes on. In prostate cancer, currently the focus of a marketing campaign by the US National Association for Proton Therapy (quote: "There was no sensation whatsoever, I feel I am healed") – a dose distribution study conducted at Harvard found proton therapy had no advantages over conventional radiation in lowering the risk of acute damage to the rectum, and a slightly elevated risk to the bladder. Low-level toxicity was somewhat reduced, "but is a late second malignancy an issue in prostate cancer?" asks Brada.

This question of clinical relevance, and the need to look at the effect of the treatment in the round, is one Brada keeps returning to. He mentions the example of the spine, where treatment with protons can be focused very precisely at the back

The imperative to invest in highly trained staff to operate this technology is a point strongly emphasised

edge of the vertebral column (see figure).

"What are the side-effects here you want to reduce?" he asks. He acknowledges that the treatment does avoid damage to the heart, "which is good, though I don't think long-term survival is necessarily determined by this." Bowel [colorectal] toxicity is also lower, "But then bowel toxicity is not a very large issue in children." His worry is about what such very precisely targeted therapy might do to the growth of the child in the longer term, and he wonders how much consideration has been given to this aspect of the treatment. "The principle would be that you treat the whole vertebral body so if there is reduced growth it is symmetrical. Now you have a new technique that only treats the back part of the verterbrae. So while you are avoiding some side-effects there are also potential risks. You need to have a very broad view. You mustn't blindly look only at the benefits you also have to measure the risks."

Brada is well aware that he is seen as Mr Negative, raining on the proton therapy parade. In fact he strongly believes that charged particle therapy will prove to be of clinical benefit in specific indications, particularly in avoiding second malignancies in some paediatric cancers and in treating cancers that respond poorly to conventional radiotherapy.

"My bottom line is that it is an interesting new treatment that should be investigated and there are specific situations where it is likely to be of benefit, but you ought to prove that it is of benefit, as you have to do with drugs. There are so many complexities to the treatment that you need to prove that the complexities and problems don't outweigh the technical benefits. I'm an academic and I'm developing new technologies, and the same rigour I require of myself I require of others."

Debus, coordinating the clinical trial platform of the ULICE project, professes a certain sympathy with Brada's argument, but points out that large randomised phase III-type studies are prohibitively expensive: "Who is going to pay?" he asks. "EMEA has big pharma behind it, and they can recoup their initial investment in the costs of the clinical studies by putting that money into the price of a drug. In medical technology you cannot put the price of studies into the price of the device."

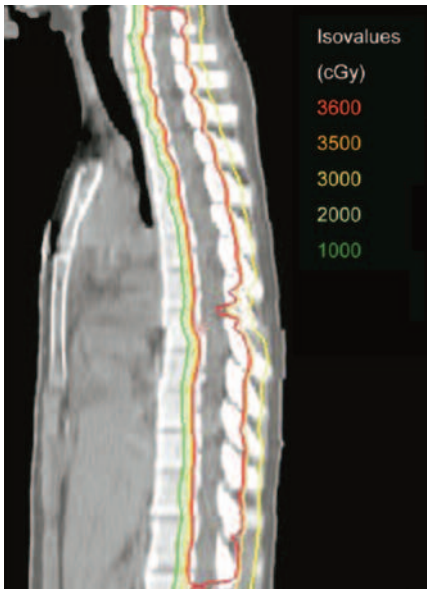
He insists, however, that the approach taken in Heidelberg, and the philosophy behind ULICE, is strongly in support of establishing robust evidence on which to base the selection of patients and tumours that can benefit from proton therapy, even if these studies can never be on the scale required for new medical therapies.

The bigger concern for Brada is what may happen outside the research community. He points towards trends in the US where five new private facilities are set to open next year, no doubt focused on large markets like prostate cancer. Will patients there have their cases discussed by a multidisciplinary team able to weigh up the best options in a disinterested way? Will they be treated by specialists who understand the disease, or simply by experts in proton therapy? Will relevant outcome measures be recorded and analysed? Or will these companies rely on the attraction of their high-tech wizardry to convince patients, and possibly doctors, that their treatment really is superior, without sufficient evidence to back up their claims?

Debus thinks it unlikely that Europe will follow this market-driven route. In Germany a decision was recently taken for proton therapy facilities to be developed at a further three university hospitals. But in the UK, where 20 years ago the proton therapy facility at Clatterbridge had taken a lead in researching this field, Brada is not so sure. Last year the government agreed to invest in a new facility, but put the job out to private contract. "Costs will have to be covered by income from the treatment, which doesn't bode well for research activities," he warns.

The current public spending cuts across Europe will make it harder to win the argument for developing particle therapy capacity within an academic, research-led framework. This makes it particularly important that the sort of inclusive, cooperative Europe-wide network currently organised within ULICE is able to continue after the programme ends in 2012, to shape and influence this area of cancer care led by evidence-based medicine and patient need.

PROTON THERAPY TO THE SPINE



This computed tomography–proton radiotherapy treatment plan shows that the back of the vertebrae will receive doses of up to 3600 cGy, while the bulk of the vertebral bodies are spared. This therapy avoids radiation to the heart and other organs in front of the spinal column, but when used in children there is a risk that, as they grow, the back part of the vertebrae will grow slower than the rest

Reprinted from Krejkarec et al. (2007) Physiologic and radiographic evidence of the distal edge of the proton beam in craniospinal irradiation. *Int J Radiation Oncology Biol Phys* 68:646–649, with permission from Elsevier

Prize for journalist who tackled taboo subject of rationing cancer therapies

Restricting access to cancer treatments is an emotive topic that politicians avoid when possible – nowhere more so than in Germany. **Nicola Kuhrt** won an award for her informative and sensitive article on this subject, entitled *Cancer therapy: What is a month of life worth?* which was originally published in the respected *Frankfurter Allgemeine Sonntagszeitung*, and is reprinted below.

20 January 2010. The holiday is desperately needed. On her doctor's advice, Anna Brinckmann has been on a 'drug holiday' for a week. It will give her a chance to recover from the side-effects of her treatment. Anna, who lives in Berlin, knows the ropes: she has already had several courses of chemotherapy with Erbitux. The drug is one of a whole group of new substances that many people see as representing the future of cancer therapy. Antibodies with special properties developed in the laboratory are designed to attack the disease with more precision than before.

Anna Brinckmann knew that around twenty per cent of Erbitux patients experience unwanted reactions. For her the side-effects always start with pus-filled pimples on her face. Her skin burns as though on fire. Even washing it with distilled water is painful. But she is also aware of the other side of the picture, with its optimistic message: the worse the skin rash, the more effectively the therapy is working. "Unpleasant, but true", was how the doctor explained it to her.

Anna Brinckmann has advanced colorectal cancer. Various studies have investigated how much longer colorectal cancer patients live if they take Erbitux. One reported a "statistically significant improvement" in survival from 20 to 23.5 months by comparison with conventional treatment; in another, patients treated with Erbitux lived on average 2.9 months longer. But what use are statistics in an individual case? Before each new course of treatment Anna Brinckmann must decide whether she wants to go on – with the hope of extending her life a little, but with the risk of severe side-effects – or whether the time has come to call a halt.

Nicola Kuhrt

It is not only the patients for whom the new, targeted drugs pose a dilemma. The new treatments cause the costs of cancer therapy to rocket. At a monthly cost of €4000 or more per drug, the annual cost per patient quickly mounts up to between

Frankfurter Allgemeine
SONNTAGSZEITUNG

Who decides what an extra month of life is worth? This well-written and sensitive feature encourages readers to join a debate on priorities for health spending that might otherwise be conducted out of the public eye by unaccountable civil servants and medical insurance bureaucrats


Fortsetzung von Seite 51

Was darf ein Monat Leben kosten?

Das Abc der Krebstherapie

€40,000 and €100,000. Surely the health system can ill afford to fund such treatments, which after all add only a few weeks to survival times?

Politicians are reluctant to address this issue. Doctors, too, hesitate to speak out. When Jörg-Dietrich Hoppe, president of the German Medical Association, forecast recently that the gap between what is medically possible and what is affordable would continue to grow, he drew criticism from all sides; the unanimous view was that his remarks were "inhumane".

But Germany will not be able to avoid the discussion of ethics and efficiency in the health service for much longer. The ageing of the population inevitably means that some therapies will at some point have to be rationed. Personalised cancer drugs could set a precedent for this.

A BOOM MARKET

Oncology is becoming the highest-turnover segment of the pharmaceutical industry. Analysts at the market intelligence company IMS Health have calculated that sales of cancer drugs by pharmaceutical companies worldwide totalled $48 billion in 2008; the figure has doubled since 2003. A further rise to $75 billion dollars is forecast by 2013.

As a result there is hardly a pharmaceutical company anywhere that is ignoring the trend and not researching at least one new cancer drug. More than 300 potential new drugs are currently in development – twice as many as for heart disease, strokes or Alzheimer's. "Innovation in medicine comes with a price tag," explains Hagen Pfundner, CEO of the leading company in the sector, Roche Pharma AG. He points out that a pharmaceutical company is a business like any other; it must pay wages and its shareholders expect to see returns. Nevertheless, Roche is investing around twenty per cent of its turnover in research, exposing itself to considerable risk in the process. "Today's innovation is tomorrow's low-cost medicine," explains Pfundner. The first drugs for tackling the AIDS virus and the early cardiovascular drugs were also very expensive, he says, but in those cases nobody talked about the price.

Cancer researchers have for years been dreaming of targeted therapies. More than a century ago the German Nobel prize winner Paul Ehrlich had the idea of preparing antibodies in the laboratory and using them to target tumours. Because of the

Germany will not be able to avoid the discussion of ethics and efficiency in the health service much longer

Roche is investing around 20% of its turnover in research, exposing itself to considerable risk

complexity of the disease, his successors are still working on putting the plan into practice: the task is difficult because tumours afford too few points of attack, cancer cells are too flexible and the emergence of resistance is too common.

There is no lack of experiments. Many of the protein molecules that have now been developed inhibit the processes that would otherwise result in the constant reproduction of cancer cells. Others interrupt signal pathways that cancer cells need to survive. Genetic tests can often determine in advance whether the drug will be effective in a particular patient or not. The therapy is then not only targeted but also 'personalised'. Marketing strategies like to refer in this context to 'made-to-measure' pills. Substances that intervene in specific processes in the tumour cell are known as 'smart molecules'.

One of the antibodies of the early days was Rituximab from Roche. This laboratory-designed protein recognises a characteristic feature on the surface of cancer cells in patients with a B-cell lymphoma. The drug, which is usually used in combination with chemotherapy, appeared on the market in 1997. It is estimated that the number of people who die from B-cell lymphoma has fallen by fifty per cent in the last ten years.

Glivec has also become well known. It has significantly improved the survival prospects of patients with a particular form of leukaemia. Over the past year Glivec alone has brought in revenue of €2.6 billion for its manufacturer, Novartis.

It is the spectacular successes of this sort that make the whole field of cancer drugs so attractive for pharmaceutical companies. On the market, however, very few of the subsequent products have yielded much real benefit for patients. "The patients live at best three or four months longer than with conventional treatment. Their quality of life is not improved," says the chairman of the German Medical Association's Drug Commission, Wolf-Dieter Ludwig. Many oncologists have been disappointed by the new drugs.

Ludwig also notes that the costs of new drugs in oncology are rising much faster than the evidence of their usefulness. In many cases there are no reliable markers for testing whether or not the targeted drug is effective. For example, for monoclonal antibodies which block the epidermal growth factor, the only guideline is often the crude

£30,000 IS THE LIMIT

The cost of a drug can vary widely from country to country. In the US and Germany pharmaceutical companies are still free to set the prices of their products themselves, but in other countries the conditions under which a drug can be marketed is usually negotiated during the licensing process.

The UK National Institute for Health and Clinical Excellence (NICE) takes a particularly firm line on this issue. The health authority evaluates new therapies in terms of QALYs – quality-adjusted life-years. A QALY is an additional year of life of good quality – the threshold is currently £30,000. If a treatment, including the drug treatment of a cancer patient, costs more than this it cannot be provided free of charge through the tax-funded British health system. In the past NICE has rejected a number of cancer drugs, including Bayer's Nexavar, used for liver cancer, the lung cancer drug Tarceva from Roche and Erbitux from Merck, which is used to treat bowel cancer.

The strict price policy of the UK health authorities has met with strong criticism from politicians and patient organisations. The protests have, however, become more muted since many pharmaceutical companies have now indicated that they are prepared to reduce their prices. For example, Celgene has agreed to provide the cancer drug Revlimid free of charge from the third year of treatment. Pfizer, too, has made concessions to the UK authorities: the kidney cancer drug Sutent is now available free for the first six-week treatment cycle. In addition, NICE has come to an agreement with the Spanish company Pharma Mar, under which Pharma Mar will cover the costs of treatment with the sarcoma drug Yondelis from the fifth treatment cycle.

DIETER RÜCHEL

principle of "If pimples, then sensitive".

Wolfgang Dietrich, head of the oncology division at Roche, describes the situation elegantly: "We haven't yet discovered the tailor-made suit, but we have the one-size-fits-all version". But tailor-made drugs are not far away – drug and diagnostics research have been running in parallel for some time. "The aim of course is to put each drug on the market complete with an appropriate marker – not to have the drug first and then run studies to discover which groups of patients it is suitable for."

However, a growing number of these studies are being terminated at a very early stage – even when there are preliminary signs of success. The pharmaceutical companies justify their action on the grounds that the therapy cannot simply be withheld from the members of the control groups who, in accordance with the study protocol, receive only a placebo. But it then becomes impossible to collect data either on the long-term efficacy of the drug or on occasional side-effects.

Costs and benefits

Further criticism comes from another quarter. According to Lilli Grell of the Medical Services Department of the Association of Health Insurance Funds (MDK), cancer studies are not now concerned with how much longer a patient lives as a result of a new drug; they only consider the length of the interval between the conclusion of treatment and return of the tumour. "It is not uncommon for a drug to extend this interval. But the patients still die just as early as those treated conventionally." And it would be wrong to believe that the innovative cancer drugs are free of side-effects. The side-effects are simply different. Whereas conventional chemotherapy was frequently accompanied by diarrhoea, vomiting and hair loss, patients must now reckon with severe skin reactions, inflammation of the brain, extreme tiredness and liver damage.

It is Grell's job to cast a critical eye over pharmaceutical innovations. The Medical Services Department for which she works is called on to make a decision when it is unclear whether statutory health insurers should cover the costs of treatment. In oncology such queries arise relatively frequently, says Grell, because cancer drugs are often used outside the approved indications – either because they are still very new, or because there are studies that suggest to doctors that the drug is worth trying. In some cases, too, a particular drug is used because the patient is already so sick that no further standard therapy is available.

Many cancer doctors prefer to say "I've got something else to try" rather than articulate the uncomfortable truth, which may be "There is nothing more I can do for you." Increasingly often, though, the request comes from patients. They read about new drugs on the Internet or in magazines and are then determined to try them.

"It needs a good relationship between doctor and patient to look at such issues together," says Annika Siegmund, a doctor at the National Center for Tumour Diseases in Heidelberg. Of course it may be possible to delay the advance of the disease, and hence the patient's death, for a certain time. "But unfortunately it is impossible to know in advance whether the treatment will be successful and how severe the side-effects will be." Sometimes, she says, one must also protect patients from themselves.

"The decisions that cancer patients now have to take are tough," explains Annika Siegmund. They ask themselves questions such as: "How much can I take, so that I have a chance of seeing my grandchild start school?" Or, "Am I actually too vain to want to battle with severe skin reactions on my face during the final months of my life?"

Anna Brinckmann from Berlin has made her decision. She wants to go on. But only one more time. "Then I will really have had enough."

This article was first published in the *Frankfurter Allgemeine Sonntagszeitung*, on 17 January 2010, and is reprinted with permission

"The costs of new drugs in oncology are rising much faster than the evidence of their usefulness"

Putting the person back into personalised therapies

The concerns of a head and neck cancer specialist

➜ Simon Crompton

With ever more biological information required to pick the perfect protocol to target an individual's disease, the hopes and the fears, the priorities, wishes and concerns of that individual risk going unheard. Listening and learning remains the key to personalising therapy, says **Jan Vermorken**, who spent a career specialising in the cruellest of cancers.

It is unusual for chickens and elephants to figure prominently in interviews with the modern movers and shakers of medical oncology. But Jan Vermorken's passion for animals is more than an idle pleasure. It's what got him involved in medicine in the first place, and parallels the compassionate model of cancer medicine that he has tried to follow for forty years.

The chickens in question roam around the grounds of the Antwerp University Hospital, where Vermorken runs a clinic once a week as emeritus professor of medical oncology, having officially retired as head of the hospital's medical oncology department last year. He sits in his portacabin office, defiantly dapper against the plasterboard, and talks about how the stubborn cockerels block his route into the car park. "They just look at me," he says. "You will not see me hurt an animal." You can imagine the queue building up behind him.

His garish silk tie, it becomes clear on close inspection, is patterned with elephants and his computer screensaver revolves pictures of the baby pachyderms, provided by his favourite charity, an elephant orphanage in Kenya. Twelve years ago, he saw them at first hand, during a visit to South Africa. "The social interaction between elephants, the way they protect their little ones, is very impressive," he says. "And the way they handle it when one of them is dying: you see them suffer. I think the interaction between them is an example of how humans should be."

Vermorken's career has spanned clinical work, research and education. He has been professor of oncology at the University of Antwerp since 1997, when he arrived in Belgium from the VU University Medical Centre in his native Netherlands. He has carried out major studies on treatments for gynae-

AEON.

cological and head and neck cancer, coordinated large trials in breast and colon cancer, and been a leading figure in the Gynecologic Cancer Intergroup (GCIG) and study groups of the EORTC (European Organisation for Research and Treatment of Cancer) and ESMO (European Society for Medical Oncology). Now, in his supposed 'retirement', he has taken up the post of editor-in-chief of ESMO's journal, *Annals of Oncology*, which he wants to change to put more emphasis on translational research and multidisciplinary working.

Looking back at how the treatment of cancer has developed over his career, it becomes clear that while he is excited by the increasing potential to individualise drug treatment, he worries about the way modern health systems work against the individualisation of care. As time-pressed doctors increasingly follow protocols and rigid systems for treating cancer, are they losing sight of that compassionate – maybe elephant-like – need to respond delicately to individual wishes? Even if it comes to hastening a person's end rather than prolonging their life? Vermorken is concerned.

Given his love of animals, it comes as no surprise that Vermorken, now 66, set out into adulthood wanting to be a veterinary surgeon. But when he started training as a vet, he realised that he would often be expected to act in the best interest of the owner, not the animal. That shocked him. In medicine it was always clear who came first, so he started medical training in 1961 so that he could put the patient truly at the centre. He graduated from the University of Amsterdam in 1970.

Maybe, he acknowledges, it was the early death of his mother from ovarian cancer in 1973 that subconsciously made him set a course in cancer medicine, and a specialisation in gynaecological cancers among others. "That was still in the days when patients were being treated with single alkylating agents, and that didn't help my mother a lot. Her quality of life was not, in the last phases of the disease, a good one. So maybe that could have played a role…"

Although his passion for animals might have originated from the regular visits to his grandparents' farm, his family did not directly influence his choice of vocation. The really important figures in his career

appeared when he started his internal medicine training at the VU University Medical Centre in Amsterdam. Vermorken worked under Lopez Cardoso, one of the first internists to be strongly involved in oncology, at a time when oncology was not the most popular option for young doctors. He arranged for Vermorken to work at the Netherlands Cancer Institute in Amsterdam in 1974.

And although Vermorken worried about the emotional toll of working with seriously ill young people, his fears diminished as he began to practise, and he began to realise that combining clinical work with research provided hope as well as variety. His commitment grew as he became a medical oncologist under Bob Pinedo, who was appointed full professor in medical oncology at the VU University and was determined to develop medical oncology in the Netherlands.

Pinedo inspired Vermorken to see the potential of medical oncology, but he also encouraged him to expand his own professional horizons, showing him the importance of the interaction between clinic and lab. This sparked a lifelong interest in translational research, and the need to balance clinical work with research.

Every patient is unique

"Pinedo taught us all that every patient is unique. You have to continually learn as much as possible from each patient, exploring all the possibilities of what you can do for them. He wasn't a man to give up easily."

It was Pinedo who encouraged him to become active in the EORTC – first in the Gynaecologic Cancer Group (GCG), and then in the Head and Neck Cancer Group (HNCG). These were the specialisms that have stayed with Vermorken throughout his career – he has been a member of the EORTC-GCG since 1980 (chairman from 1983 to 1989) and a member of the EORTC-HNCG since 1985 (chairman from 2006 to 2009).

"We did a lot within EORTC in the earlier days," he says. "We wrote an enormous number of protocols. Conducting trials has become very complex nowadays, and it's difficult for EORTC to keep the same pace. But in those days there were far fewer administrative hurdles, and we wrote one protocol after another and also got them running. We were a group of friends who were willing to really work for each other, so it was great, great fun – and very rewarding."

"In the 1980s, there were tremendous changes in the treatment of these cancers. When I started, radiotherapists and head and neck surgeons were certainly the leading figures in head and neck cancer – and they still are to some extent because their therapies are crucial for this disease. But I think that the integration of systemic therapies over time has become more and more important, and medical oncology – which is a young profession – has gained standing."

Head and neck cancers, he says, have never been the most popular career choice for medical oncologists. It's not just the fact that systemic therapies were not so integral to the treatment of these usually late-diagnosed cancers. It's the less palatable fact that these cancers disproportionately affect less privileged members of society – heavy smokers and alcoholics for example – and that the aggressive treatments they usually require are often highly toxic and sometimes mutilating.

And now, he says, the increasing efficacy of cancer drugs to help control the disease is bringing its own problems. "I think it's the worst kind of cancer you can think of," says Vermorken. "For patients with advanced disease – which is about two-thirds of those diagnosed – the treatment has changed from using local therapies only to a combined modality approach, with a tendency in some countries to be primarily non-surgical. Now, as we're seeing the effectiveness of this grow, we're also beginning to understand that the late side-effects of these non-surgical approaches might strongly influence quality of life and might even be killing some."

There have been, he stresses, spectacular advances in the treatment of cancer since he came into oncology, and many have had a positive impact on head and neck and gynaecological cancers. New targeted therapies have a lower toxicity profile and may be combined with existing therapies

He worries about the way modern health systems work against the individualisation of care

"You must learn as much as possible from each patient, exploring all possibilities of what you can do for them"

Inspiring a new generation. Vermorken and his colleagues at Antwerp University Hospital hosted the first Elective Course in Oncology for Medical Students, sponsored by the EU and FECS (now ECCO), August 2005

such as radiation therapy and chemotherapy.

And although, until recently, there had been few targeted drug breakthroughs for head and neck cancers, trials coordinated by Vermorken have shown for the first time that patients with recurrent and/or metastatic head and neck cancer have a significantly improved outcome with the use of the monoclonal antibody cetuximab, when given in combination with platinum-fluorouracil chemotherapy. "I'm very happy that, after 30 years, we've finally found a way to give a better result to these patients," he says.

A different type of targeted care

He argues, however, that the fundamental challenge facing cancer doctors are not changed even by the advent of new targeted therapies. If they really want to serve the best interests of the patient, and to make sure that care is right for the individual, then sometimes the obvious treatment may not be the best option at all. Maybe a different kind of targeted care is required.

"Personally, I think we are sometimes too eager to administer medication to patients. That may be good in the curative setting, but is sometimes questionable in the palliative setting. We know that the biological behaviour of some of the tumour types is quite variable, and it is wise to see how rapidly a tumour is growing before administering medication – because it should be clearly understood that there is no effective medication without side-effects. I have many examples of patients with cancer who came to me for a second opinion, having been advised to receive chemotherapy,

and it was clear that it could be years before they needed it because the tumour was not aggressive."

When the cancer is advanced, the challenge of doing the right thing for the individual becomes even greater. "For people who are dying, the medical oncologist can help these people by not running away when things become difficult. And what I mean is, for example, active euthanasia."

Vermorken remembers the days when physician-assisted euthanasia was not officially legal (it was legalised in Belgium in 2002), and subsequent police questioning: "talking to you as if you were a criminal," he says. But he will also never forget a woman with end-stage head and neck cancer who asked for euthanasia, and said, just before the drugs were administered, "Please do it as quickly as possible."

"She didn't want to gradually go to sleep. What we said didn't matter to her. Her suffering was so tremendous, and that made an enormous impression on me. I'd never seen someone so longing for the end of life, and I think doctors should never walk away from this."

In fact, Vermorken believes that if doctors talk openly to their patients about euthanasia, it worries them less, and they are unlikely to pursue it as an option. "It's a strange thing. The moment you make clear you are not running away from it, and you will be at their side until the end, it's very often sufficient."

It's not that Vermorken is a passionate advocate of euthanasia – which is, of course, not an option in most countries. But the importance of sitting and listening to patients is a permanent theme throughout our interview. "I'm worried that doctors today are so rushed that they can't listen and learn about the individuals they're treating and what they want. But you will only be a good doctor if you do so. Patients aren't a form to be filled in."

These are principles Vermorken carries through to his teaching work. As well as courses in cancer medicine at the Antwerp University Hospital, he has run various summer schools for medical students since 2004, backed by universities throughout Europe, which, he hopes, have stimulated interest in cancer medicine – whether it be surgery, radiotherapy or oncology.

Teaching students to listen

The most enlightening moments on the courses come when students have to interact with patients who tell them about the impact that health care professionals can have at such a difficult time in their life. "You can see the students beginning to lose their fear, and begin to discuss things more openly with patients."

A key theme in his teaching has been the importance of multidisciplinary work. As a specialist in the field of head and neck cancer and gynaecological cancer, where combinations of treatment are often key, Vermorken knows that feeding in the perspectives of different disciplines into decision-making processes can only benefit the patient.

He has little time for the professional turf wars that have been fought in some European countries over, for example, who should lead care in gynaecological cancers.

"There are differences from country to country," he says. "In the Nether-

Still looking ahead. Even in retirement Vermorken remains an important presence at conferences like this one in Beirut, January 2010, where he gave a presentation on future directions in head and neck cancer treatment

"The medical oncologist should be part of this decision-making process from very early on"

"It has shown to me that the immunological response in the body to tumour cells is absolutely of importance"

lands, there is the discipline of gynae-oncology – gynaecologists who have specific surgical training and skills in major surgery, such as debulking surgery in patients with advanced ovarian cancer. Preferably, patients with gynaecological cancer should be treated by such specialist colleagues. But when there are many treatment options, these need to be discussed by a panel of experts, each of them making full use of each other's expertise, and entrusting patients to those with most experience in a particular field. The medical oncologist should be part of this decision-making process from very early on."

Although Vermorken has never worked in a laboratory, his research work has been significant, and he's particularly proud of three areas of work. One is the clinical research that led to the first improvement in outcome of patients with recurrent and/or metastatic head and neck cancer. He hopes the successful cetuximab trial will now lead to further treatment developments.

A second area is the introduction of a new form of induction chemotherapy, including docetaxel (the so-called TPF regimen), for patients with advanced head and neck cancer that cannot be removed by surgery. His research on this was published in 2007. The improved outcome of these patients led to a revival of induction chemotherapy in head and neck cancer and has strongly influenced the type of studies now being conducted in the advanced disease setting.

A question of immunology

His third research achievement is possibly the one that has had least impact, but may also have the most potential. In the 1990s, Vermorken coordinated a study investigating whether vaccinating survivors of colon cancers using vaccines derived from their own cancer cells reduced the risk of recurrence. It seemed to, but the findings were never confirmed by others: "For a variety of reasons," says Vermorken. "Logistics, complicated procedure, financial hurdles … But I think it was a proof of concept. It has shown to me that the immunological response in the body to tumour cells is absolutely of importance."

With grandchildren Beau, 7 months, and Claire, 6 months

Vermorken loves working with people and enthusing students about medical oncology, so in his retirement he's as busy as ever – finding a time to speak to him at all is a feat. He's still attending cancer conferences, organising symposia, running an annual international medical oncology course, participating in or running summer schools with ESO and ECCO, running post-ASCO meetings in Belgium and chairing the Belgian Association for Cancer Research. He is also a member of journal editorial boards, and still active in the EORTC-HNCG group and many other committees of national and international cancer organisations.

His family – wife, two grown-up sons, and two grandchildren – understand that his work is his hobby, and always will be. So though he is looking forward to spending more time with his wife at his holiday house in their beloved France, enjoying the good food, he acknowledges that he'll probably be looking through some journal papers while he's sipping his fine wine. And one day he will find time to return to Africa, to meet those formidable, caring elephants again, face to face.

Neoadjuvant trial design: time for a brave new world?

Heather McArthur and Clifford Hudis

In the NOAH clinical trial, trastuzumab treatment for locally advanced breast cancer, given prior to surgery, was associated with increased complete and overall response rate and improved event-free survival. The ability to identify this advantage suggests that the neoadjuvant setting might serve to inform the design of adjuvant trials and indicate appropriate off-study adjuvant therapy.

Locally advanced breast cancer (LABC) has not been consistently defined; however, it generally denotes inoperable tumours that are large, have extensive lymph node and/or skin or chest wall involvement as well as typically including the rare and aggressive inflammatory breast cancer subtype. LABC is associated with a worse prognosis than operable early-stage disease, but a better prognosis than metastatic disease.[1] Historically, patients with LABC were treated with modified radical mastectomy and radiotherapy alone, but with disappointing results. Thereafter, systemic therapy became an integral component of the LABC management strategy, largely as a consequence of the promising results reported with adjuvant systemic strategies in the early-stage breast cancer setting. Specifically, the administration of systemic neoadjuvant therapy before definitive surgery and radiotherapy induced tumour response and improved local control rates. The practice of delivering neoadjuvant chemotherapy, hormone therapy and/or biologic therapy affords a number of potential advantages, including downstaging of the primary tumour to allow for surgery and, in some cases, increasing the likelihood of a breast-conserving approach. From a research and therapeutic innovation perspective, because pathology is obtained at diagnosis and again at definitive surgery, neoadjuvant strategies permit a convenient and *in vivo* assessment of response to specific systemic therapies. Furthermore, because the event rates are higher in LABC than in early-stage disease, the follow-up time and the sample size required for LABC studies are typically modest in comparison. For these reasons, the neoadjuvant study model offers tremendous promise as an efficient drug development tool.

Up to 20% of breast cancers present with either amplification of the *HER2* gene or overexpression of its protein product, a transmembrane receptor tyrosine kinase, and are considered to be 'HER2-positive'. Trastuzumab is a humanised HER2-targeted monoclonal antibody that was developed through traditional translational drug development pathways. It was first studied *in vitro* and in animal models, then as monotherapy in phase I and II trials in patients with metastatic breast cancer,[2–4] then in combination with chemotherapy in randomised trials in the metastatic setting.[5] Ultimately it was tested in combination with proven adjuvant chemotherapy strategies,[6,7] where its use was associated with significant survival improvements.

The impact of treatment with trastuzumab in the LABC setting was recently evaluated in the NOAH study, an international, open-label, phase III trial.[8] The NOAH trial was originally designed to randomise women with HER2-positive, locally advanced or inflammatory breast cancer to neoadjuvant trastuzumab plus chemotherapy followed by adjuvant trastuzumab or to neoadjuvant chemother-

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apy alone. However, when the results from the first adjuvant trastuzumab studies were reported,[6,7] the trial design was altered so that 19 of the 118 women (16%) with HER2-positive breast cancer randomised to the chemotherapy-alone arm were offered a standard course of adjuvant trastuzumab (with analyses performed by intention-to-treat). This trial was unique in that it included an observational cohort of 99 women with HER2-normal LABC for comparison. After a median follow-up of 3.2 years there were significant improvements in the overall response rate (ORR), including a doubling of the total pathologic complete response (pCR) rate, and the event rate in the cohort receiving neoadjuvant trastuzumab and chemotherapy compared with those receiving chemotherapy alone. Specifically, for the 117 women who received chemotherapy with trastuzumab versus the 118 women allocated to receive chemotherapy alone, the pCR rate was 38% versus 19% (P=0.001), the ORR was 87% versus 74% (P=0.009), and the hazard ratio for event-free survival (EFS) was 0.59 (P=0.013) in favour of the trastuzumab arm. However, consistent with numerous other neoadjuvant reports, the improvements in pCR, ORR and EFS rates did not translate into overall survival benefits. Thus, the NOAH investigators appropriately concluded that, although the administration of neoadjuvant trastuzumab improved pCR rates, it is unknown whether the observed EFS benefits can be ascribed to the administration of neoadjuvant trastuzumab, adjuvant trastuzumab or the combination. Although to our knowledge there are no planned studies comparing EFS rates with neoadjuvant trastuzumab, adjuvant trastuzumab or the combination in LABC, such a study would not only inform LABC treatment recommendations but could also indirectly inform decisions in the early-stage setting where the optimal duration of trastuzumab treatment is not established.

It is now more than 20 years since the association between HER2 status and risk of relapse and death was published[9] so why did it take 20 years to get to this stage? While the results from the NOAH study were predictable (that is, trastuzumab confers benefits in HER2-positive LABC as it did in HER2-positive early-stage and metastatic breast cancer), it nonetheless leaves us with more questions than answers: Should trastuzumab be administered before surgery, after surgery or both? What is the optimal chemotherapy regimen for coadministration? Were there any biologic predictors of response or resistance to therapy? How will other promising HER2-targeted agents be incorporated into the LABC management strategy? Is there a more efficient paradigm for the timely evaluation of novel, promising therapeutic innovations? Would improved drug development paradigms have positively impacted the design and implementation of modern neoadjuvant studies of other HER2-targeted agents, including the tyrosine kinase inhibitor lapatinib (as in NeoALLTO, NSABP B41 and CALGB-40601) and the monoclonal antibody pertuzumab (as in NEOSPHERE)? How can we learn from our experiences so that novel HER2-targeted agents with promising activity in the metastatic setting (such as T-DM1 and HSP90 inhibitors) are evaluated efficiently?

Using traditional drug development strategies, it is difficult to fathom how we will begin to tackle the seemingly exponential growth of clinical questions. Possibly, the traditional model of drug development, whereby drugs are moved from the lab through a series of phase I to III studies in the metastatic setting before moving into the adjuvant setting and beyond, is too labour intensive, costly, inefficient and slow. Does the answer lie in the advantages and conveniences of the LABC model? If so, will we ever be brave enough to shed the traditional study paradigms, eliminate metastatic studies altogether (at least as a necessary step before neoadjuvant trials) and adopt a primary neoadjuvant study model? Imagine if the NOAH trial and the smaller neoadjuvant trastuzumab–chemotherapy study from MD Anderson Cancer Center[10] had been conducted at the onset of trastuzumab development, in all likelihood the adjuvant studies would have been conducted earlier, novel HER2-targeted therapy development may have been accelerated, and biologic-correlate studies might have advanced our understanding about HER2-positive disease faster. Certainly a paradigm shift is not without its challenges and drastic change will always be met with resistance, but it must be time to seriously consider such a brave new world!

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

Practice point

Since drug development in the metastatic breast cancer setting often relies on endpoints (such as response rate and progression-free survival) that are either loosely linked to overall survival or poorly predictive of ultimate activity in the adjuvant setting, novel approaches are needed. To the degree that in-breast response (such as pathologic complete response) can serve as a surrogate for progression-free survival and overall survival in the early-stage setting, neoadjuvant (preoperative) trials may facilitate faster and more efficient identification of promising new systemic therapy regimens.

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Are macrophages the bad guys in Hodgkin lymphoma?

Volker Diehl

Prognostic models for patients with Hodgkin lymphoma are imperfect and do not allow a precise individualised therapy. A recent gene-expression profiling study, translated into a routine immunohistological test, identified genes of tumour-associated macrophages as being responsible for treatment outcome in patients with Hodgkin lymphoma. If this finding is confirmed by other investigators, it could be a major step towards personalised therapy for patients with Hodgkin lymphoma.

Patients with Hodgkin lymphoma (HL) with early-stage disease are cured in >95% of cases, and in patients with intermediate-stage and advanced-stage disease, cure rates of 80%–90% are achieved with modern treatment strategies consisting mainly of polychemotherapy with or without radiotherapy. In the future, these treatments might be complemented by therapies based on small molecules and antibodies.[1] This unusual success rate in the treatment of an adulthood cancer, however, is associated with an inevitable burden of overtreatment and undertreatment of at least 10%–20% of patients in all stages of disease, which can result in unnecessary early progression or late toxic effects. Since the pathognomonic Reed–Sternberg cells (0.1%–1.0% at diagnosis) and the surrounding so-called 'innocent bystander cells'[2] are very sensitive to chemotherapy and radiotherapy, more than 90% of patients with HL experience a first complete remission at onset. However, 20%–30% of the tumours will progress or relapse. These failures cannot be predicted with certainty using available clinical, biological or molecular biomarkers.

Currently, there are two strategies that aim to tailor therapy at diagnosis on the basis of response and outcome prediction for the individual patient, which are not robust measurements. The first is risk adaptation, in which the clinical and biological International Prognostic Score is used for advanced-stage

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disease,[3] or the Ann Arbor classification and tumour burden that is used in early-stage disease. The second strategy is response modulation, in which therapy is escalated or reduced according to the FDG PET/CT result after two courses of induction therapy.[4] Both strategies are applied in ongoing international HL trials, yet they are far from offering the necessary accuracy to provide a personalised treatment option for individual patients.

The recent study by Steidl et al.,[5] however, opens a new hopeful avenue to reach the goal of personalised medicine. In this publication, the authors describe a method for predicting HL outcome by applying a frequently used but often-underestimated pathology test.

The researchers (a combination of pathologists, molecular biologists, biostatisticians and clinicians) measured the amount of CD68+ macrophages in the primary tumour lesions of patients with HL and correlated the percentage of CD68+ macrophages (immunohistochemical score 0–3) to the outcome of therapy.

This association was relevant for the induction treatment phase. Furthermore, the quantity of CD68+ tumour-associated macrophages predicted success or failure in the setting of disease-relapse after autologous haematopoietic stem-cell transplantation.

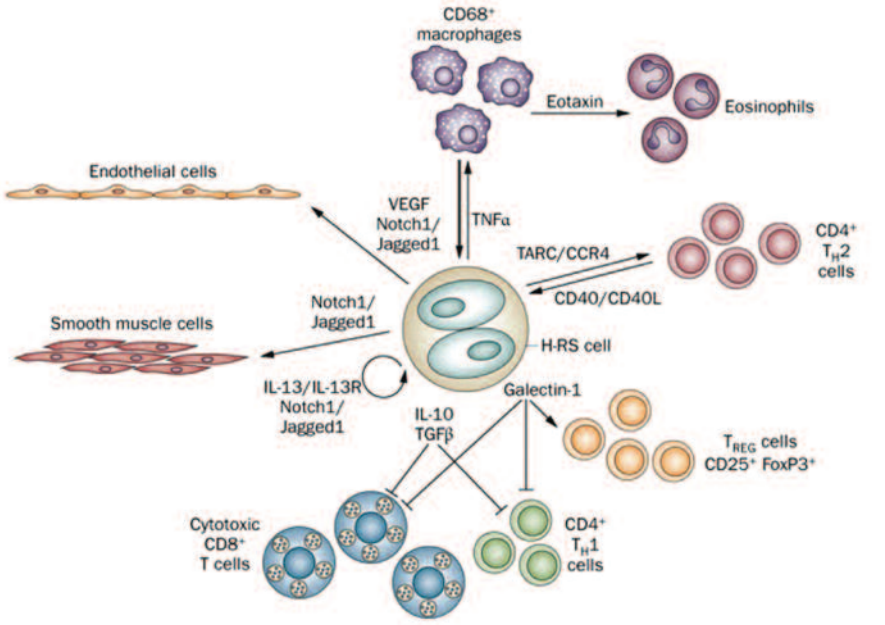
Gene-expression profiling studies on a set of 130 frozen biopsy samples revealed a group of genes that showed a significant correlation between the gene-expression profile and the outcome of primary and secondary treatment. The validity of these findings was confirmed in an independent cohort of 166 patients with classic HL, using immunohistochemical analysis of tumour tissue on paraffin blocks.

These findings, along with previous studies,[6,7] revealed three major factors that correlate with the failure of primary HL therapy: the abundance of tumour-infiltrating macrophages, the lack of small B-lymphocytes, and the overexpression of metallopeptidases (such as MMP11).

Steidl et al.[5] focused on the CD68+ macrophages because of the strong signals from the gene-expression data and the prominent role of macrophages in the process whereby tumour cells interact with bystander cells, such as macrophages, eosinophils, mast cells, B-cells and T-cells (see figure). These interactions lead to an inhibition of apoptosis, which increases proliferation and promotes the survival of tumour cells, not only in HL but also in follicular non-HL,[8] as well as in other B-cell malignancies.[9]

The immunohistochemical macro-

INTERACTION OF H-RS CELLS WITH THE MICROENVIRONMENT



The interactions between H-RS cells and the microenvironment include mediators and reactive innate immunity bystander cells. CD68+ macrophages are activated by TNFα and the fragile H-RS cells are regulated by mediators such as Notch1/Jagged1, and by the angiogenic switch, which is controlled by VEGF in conjunction with endothelial and smooth muscle cells. H-RS cells attract CD4+ lymphocytes via TARC/CCR4 and interact with the CD4- cells via CD40–ligand interaction. Cytotoxic CD8+ T-cells and CD4+T_H1 cells are kept at a distance from the H-RS cells and inhibited by IL-10, TGFβ and galectin-1, which in turn activates CD25+ FoxP3+ T_{REG} cells. A paracrine loop via IL-13/IL-13R assisted by Notch1/Jagged1 promotes proliferation of H-RS cells.

CCR4 – chemokine receptor 4; H-RS – Hodgkin-Reed–Sternberg; IL-10 – interleukin-10; TARC – thymus and activation-regulated chemokine; TGFβ – transforming growth factor-beta; TNFα – tumour necrosis factor-alpha; T_{REG} cells – T-regulatory cells; VEGF – vascular endothelial growth factor

phage score in the primary tumour lesion of patients with HL not only predicted the outcome in advanced stages of the disease but, furthermore, indicated a 100% chance of long-term, disease-specific survival in the absence of an increased number of CD68+ cells. Moreover, in advanced stages of classic HL, this molecular adverse prognostic factor significantly outperformed the International Prognostic Score for disease-specific survival (P=0.003 vs P=0.03, respectively).

The important question is whether these findings will have a notable impact on general practice in the management of HL patients?

As DeVita and Costa[10] point out, it is of pivotal importance that a personalised treatment strategy is developed in the future treatment of patients with HL, to identify at diagnosis those individuals with increased resistance to chemotherapy and radiotherapy, thus enabling clinicians to adjust the quality and quantity of drug combinations for individual patients.

This pioneering study, however, was a retrospective analysis, and confirmation of the results by other investigators is needed to ascertain the validity of these findings in a large number of patients and in a prospective setting – especially when treating patients with advanced-stage disease with a more aggressive regimen, such as escalated-dose BEACOPP.

An additional future requirement will be to translate this diagnostic method into a treatment strategy to allow a prognostic allocation of patients. Further studies will also need to consider whether the determination of the number of CD68+ macrophages in the tumour lesion of a patient with HL will be sufficient to predict outcome, or whether an accurate prediction will also depend on measurement of the B-cell content and the MMP11 metallopeptidase activity.

It seems likely that this information could gain widespread use, since the determination of CD68+ tumour-associated macrophages by immunohistology is already a routine test for diagnosis of classic HL in most experienced haematopathology institutions. Furthermore, since the necessary techniques are already established in most laboratories, it is cost-effective and reproducible.

Many pathologists have described CD68+ macrophages in the biopsies of patients with classic HL, and many clinicians in recent years have read this information in their pathology reports. Why then was this association not recognised earlier and used to predict outcome as a simple, frequently used test?

Possibly, the simple answer is that clinicians and pathologists did not put the pieces of this molecular-biological puzzle together as Steidl et al.[5] have now done. Indeed, this study is an excellent example of interdisciplinary collaboration, often referred to as 'translational research' or 'patient-oriented research', which reaches from the bench to the bedside!

Practice point

In a recent study, a frequently used immunohistologic diagnostic test was used to measure the amount of CD68+ macrophages in the primary tumour lesions of patients with Hodgkin lymphoma. This macrophage score not only predicted outcome of therapy in disseminated stages, outperforming the International Prognostic Score (IPS), but also predicted outcome in localised stages and indicated a 100% chance of long-term disease-specific survival when the score was low.

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NEWSROUND

Selected reports edited by Janet Fricker

Nilotinib and dasatinib superior to imatinib in first-line CML treatment

➜ New England Journal of Medicine

After one year of treatment, nilotinib and dasatinib were both found to be superior to imatinib when used as initial therapy for chronic myeloid leukemia (CML) with respect to all endpoints, according to two separate phase III studies.

Imatinib, an inhibitor of the BCR-ABL kinase, is the standard first-line therapy for patients with chronic-phase CML. Eight-year follow-up of the IRIS study revealed that responses to imatinib were durable and have an acceptable adverse-event profile, with an estimated rate of overall survival of 85%. But in addition to a relatively low potency, imatinib is susceptible to resistance through a large number of different mutations in the BCR-ABL target as a consequence of the way it binds to the BCR-ABL kinase domain. Two second-generation BCR-ABL kinase inhibitors have been developed that are more potent than imatinib, and have activity against most imatinib-resistant mutations in BCR-ABL. Dasatinib and nilotinib have been approved as second-line treatments for patients with CML if imatinib therapy fails. The current studies were undertaken to compare dasatinib and nilotinib with imatinib in the first-line setting.

In the Dasatinib versus Imatinib Study in Treatment-Naïve CML Patients (DASISION) Hagop Kantarjian and colleagues, from the MD Anderson Cancer Center in Houston (Texas), randomised 519 patients with newly diagnosed chronic-phase CML, from 108 study centres in 26 countries, to dasatinib (100 mg once daily; *n*=259) or imatinib (400 g once daily; *n*=260). The rate of major molecular response was 46% for dasatinib versus 28% for imatinib (*P*<0.0001); and progression to the accelerated or blastic phase of CML occurred in 1.9% of those receiving dasatinib versus 3.5% on imatinib. Safety profiles for the two treatments were found to be similar.

"In our trial, dasatinib, as compared with imatinib was associated with significantly higher and faster rates of complete cytogenetic response and major molecular response. Given the established association between complete cytogenetic responses within the first 12 months after the initiation of imatinib therapy and superior long term progression-free survival, longer follow-up may show that dasatinib therapy improves the long-term outcomes in patients with newly diagnosed chronic-phase CML," write the authors.

In the Evaluating Nilotinib Efficacy and Safety in Clinical Trials – Newly Diagnosed Patients (ENESTnd) study, Giuseppe Saglio and colleagues, from the University of Turin (Italy), randomised 846 patients with newly diagnosed Philadelphia chromosome-positive chronic-phase CML to receive nilotinib twice daily (300 mg *n*=282; 400 mg *n*=281) or imatinib 400 mg once daily (*n*=283).

Results at 12 months show that the major molecular response was 44% for 300 mg nilotinib, 43% for 400 mg nilotinib and 22% for imatinib (*P*<0.001 for both comparisons). The rates of complete cytogenetic response by 12 months were significantly higher for nilotinib (80% for the 300 mg dose and 78% for the 400 mg dose) than for imatinib (65%) (*P*<0.001 for both comparisons). Patients receiving either the 300 mg dose or the 400 mg dose of nilotinib twice daily had a significant improvement in the time to progression to the accelerated phase or blast crisis, as compared with those receiving imatinib (*P*=0.01 and *P*=0.004, respectively).

It is clear, write the authors, that nilotinib is more effective than imatinib. "Further follow-up will provide information on the durability of responses, the development of treatment resistance, and the side-effect profile of nilotinib in the front-line setting," they conclude, adding that studies will also be necessary to evaluate cross-resistance mechanisms, sequencing of treatment options and combinations of agents.

In an accompanying commentary Charles Sawyers, from Memorial Sloan-Kettering Cancer Center in New York, writes, "Some observers may argue that 1 year is too early in the comparison to claim victory in a disease with a much longer natural history, but early, sustained complete cytogenetic response is a validated surrogate marker for survival in CML on the basis of previous trials of interferon."

There are modest differences in side-effects, he adds, that might lead patients to switch from one drug to another. "There have been associations with pleural effusions with dasatinib, biochemical changes in liver function and QT prolongation with nilotinib, and edema and mus-

cle cramps with imatinib. Ironically, imatinib may survive the challenge on the basis of economic rather than scientific factors, since it could be available in generic form as early as 2014."

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Adding heat improves chemotherapy results in sarcoma

➔ Lancet Oncology

Treating high-risk sarcoma patients with regional hyperthermia alongside chemotherapy was associated with a 42% reduction in the risk of local progression or death compared with chemotherapy alone, reports a phase III German study.

The rationale for using regional hyperthermia is that heat kills cells by direct thermal toxicity, thereby increasing the efficacy of chemotherapy and inducing tumouricidal immune responses. In randomised trials combining regional hyperthermia with radiotherapy, locoregional control and disease-free survival has been improved in patients with melanoma, recurrent breast cancer and cervical cancer.

Between July 1997 and November 2006, Rolf Issels and colleagues, from the University Hospital in Munich, Germany, randomised 341 patients, from eight centres across Europe and one centre in the US, to receive neoadjuvant chemotherapy of etoposide, iphosphamide, and doxorubicin alone (n=172) or combined with regional hyperthermia (n=169). Patients had adult-type soft-tissue sarcoma of at least 5 cm diameter, grade 2 or 3, deep to the fascia but with no evidence of distant metastases. Regional hyperthermia was undertaken with a system (BSD-2000) using radiofrequency to reach a target tumour temperature of 42°C (107°F) for 60 minutes on days one and four of each chemotherapy cycle during induction and post-induction therapy.

Results show that at two years the primary endpoint of progression-free survival was achieved in 76% of the hyperthermia group versus 61% of the chemotherapy-alone group (P=0.003). Secondary endpoints were also significantly better for the hyperthermia group. Disease-free survival was nearly double that of chemotherapy alone (32 vs 18 months, P=0.011), and the treatment response rate was more than double (28.8% vs 12.7%, P=0.002).

However, the addition of hyperthermia significantly increased the risk of leukopenia, (reported in 77.6% of the hyperthermia group versus 63.5% of the chemotherapy-alone group, P=0.005), and thrombocytopenia (17.0% vs 13.8%, P=0.42). This, the authors suggest, may be related to the heating field involving part of the bone marrow, especially in patients with large abdominal or pelvic tumours. Other hyperthermia-related adverse events included pain, bolus pressure and skin burn, which were mild to moderate in 40.5%, 26.4%, and 17.8% of patients, and severe in 4.3%, 4.9% and 0.6%, respectively.

"This therapeutic strategy offers a new treatment option and can be integrated in the multimodal treatment approach for these patients," conclude the authors.

"Whether a similar benefit will be seen in lower risk patients, and whether the safety profile will be the same, and hence the trade off between benefit and harm worthwhile, remains to be established."

In an accompanying editorial, Robert Benjamin, from the MD Anderson Cancer Center, said that there were questions over whether the findings could be extrapolated for widespread use, or whether the technique should be limited to centres of excellence. Additionally, patients with atypical lipomatous tumours (ALT; also known as well-differentiated liposarcomas) had been excluded from the trial, he added, making it important to undertake such studies before "hyperthermia can take its place in standard sarcoma management. A more contemporary preoperative and postoperative chemotherapy regimen could be included for those with high-grade tumours."

■ RD Issels, LH Lindner, J Verweij et al. Neo-adjuvant chemotherapy alone or with regional hyperthermia for localised high-risk soft-tissue sarcoma: a randomised phase 3 multicentre study. *Lancet Oncol* June 2010, 11:561–570

■ RS Benjamin. Regional hyperthermia: new standard for soft-tissue sarcomas? *ibid* pp 505

Shark cartilage delivers no benefit in lung cancer

➔ JNCI

The anti-cancer drug AE-941, a shark cartilage derivative, does not improve overall survival in patients with inoperable stage III non-small-cell lung cancer, a study sponsored by the US National Cancer Institute has found.

The absence of blood vessels in shark cartilage, in addition to preclinical studies analysing cartilage extracts, have supported the hypothesis that cartilage contains inhibitors of angiogenesis. In 1993 the US television news programme *60 Minutes* ran a story about use of shark cartilage as a cancer therapy, and by 1997 prominent complementary and alternative medicine practitioners were recommending its use to cancer patients. More recently, surveys have suggested that 6%–25% of cancer patients now use shark cartilage.

Charles Lu and colleagues, from the MD Anderson Cancer Center, write that the impetus for undertaking the current randomised double-blind trial on shark cartilage comes from, "The widespread use of poorly regulated complementary and alternative medicine products, such as shark cartilage-derived agents, among patients with advanced cancer, a population likely to be vulnerable to unsubstantiated marketing claims."

Between June 2000 and February 2006, the investigators enrolled 379 newly-diagnosed untreated stage 3 non-small-cell lung cancer patients at 53 sites in the US and Canada, who

received standard treatment of induction chemotherapy and chemoradiation, and were randomised to be treated with either AE-941 (*n*=188) or placebo (*n*=191), both in the form of a liquid. Patients drank four ounces of the extract twice daily.

Results at a median follow-up of 3.7 years show that no difference was seen in overall survival, progression-free survival, time to disease progression and tumour response rates between the groups receiving AE-941 and the groups receiving placebo. The median survival period was 14.4 months (95%CI 12.6–17.9 months) in patients who received AE-941 versus 15.6 months (95%CI 13.8–18.1 months) in patients who received placebo (*P*=0.73). Furthermore, no differences between the two groups were observed in common toxic effects of grade 3 or higher, attributable to chemoradiotherapy.

"The addition of AE-941 to chemoradiotherapy did not improve overall survival in patients with unresectable stage III NSCLC. This study does not support the use of shark cartilage-derived products as a therapy for lung cancer," conclude the authors. " We hope that this trial will provide physicians with relevant evidence-based information that can be conveyed to cancer patients who inquire about the activity of shark cartilage in their disease."

AE-941, the authors add, was manufactured and developed as an anticancer drug. "Therefore, these results represent the highest level of clinical data available for the role of a shark cartilage-derived agent as a cancer therapy," they write, adding that a further strength of the study is that subjects were recruited from both academic and community oncology centres, thereby enhancing the generalisability of the findings.

One limitation of the study, write the authors, was the lack of available pharmacokinetic and pharmacodynamic correlative studies, which limited their ability to investigate explanations for AE-941's lack of activity. "AE-941 is a standardized extract of a natural product, and currently, the active molecules in this extract remain poorly understood. Therefore there have been no human pharmacokinetic studies or validated pharmacodynamic or predictive biomarkers of activity."

In an accompanying editorial Jeffrey White, from the Division of Cancer Treatment and Diagnosis at the National Cancer Institute, said, "The results of the current trial provide valuable information to health-care practitioners and patients for discussions about the use of shark cartilage in cancer management."

He added that questions might arise about the generalisation of these findings to other, or all, shark cartilage products, and the study was missing important information about the process of standardisation, the variability in the product, best dose and compliance.

■ C Lu, JJ Lee, R Komaki, et al. Chemoradiotherapy with or without AE-941 in stage III non-small cell lung cancer: a randomized phase III trial . *JNCI* 16 June 2010, 102:859–865

■ J White. The challenge of rational development of complex natural products as cancer therapeutics. *ibid* pp 834–835

Once-only flexible sigmoidoscopy reduces colorectal cancer incidence and mortality

➔ The Lancet

Offering single flexible sigmoidoscopy examinations to individuals aged between 55 and 64 reduced the incidence of colorectal cancer by 33% and mortality by 43%, UK investigators report.

Colorectal cancer is the third most frequently diagnosed cancer worldwide, accounting for more than 1 million cases and 600,000 deaths every year. Since survival is strongly related to stage at diagnosis (with survival rates of 90% for localised cases) this highlights the importance of screening. Many countries currently offer biennial screening with faecal occult blood tests, which are estimated to reduce mortality by around 25%. Since most colorectal cancers arise from adenomas, two-thirds of which are located in the rectum and sigmoid colon, Wendy Atkin and colleagues from Imperial College in London, UK, set out to evaluate the benefits of one-time flexible sigmoidoscopy screening on the incidence of colorectal cancer and its associated mortality.

In the study, which took place in 14 centres in the UK, 170,432 men and women, aged between 55 and 64 years, were randomised to either the intervention group, who received flexible sigmoidoscopy (*n*=57,237), or to a control group who received no intervention (*n*=113,195). In order to take part in the study, subjects needed to be registered with participating general practices and to have indicated on previous questionnaires that they would accept an invitation for screening. Participants underwent flexible sigmoidoscopy with polypectomy for small polyps and referral for colonoscopy if they had polyps measuring 1 cm or larger, three or more adenomas, tubulovillous or villous histology, severe dysplasia or malignant disease.

Results show after a median follow-up of 11.2 years, 2524 participants were diagnosed with colorectal cancer (1818 in control group versus 706 in the intervention group) and 20,543 died (13,768 in the control group versus 6775 in the intervention group).

In intention-to-treat analyses, colorectal cancer incidence in the intervention group was reduced by 23% (HR 0.77, 95%CI 0.70–0.84) and mortality by 31% (HR0.69, 95%CI 0.59–0.82). Those who attended their invited screening session (ie disregarding those who did not attend) had a 33% lower risk of a colorectal cancer diagnosis than those in the control group (HR 0.67, 95%CI 0.60–0.76), and a 43% lower risk of death from colorectal cancer (HR 0.57, 95%CI 0.45–0.72). Furthermore, the researchers estimated that 489 people would need to be screened to prevent one death due to colorectal cancer.

"The results from our trial show that flexible sigmoidoscopy is a safe and practical test and, when offered only once to people between ages 55 and 64 years, confers a substantial and long lasting protection from colorectal cancer," conclude the authors.

A limitation of the trial, they add, is that rather than inviting the whole population aged 55–64 years for screening, the trial used a two-stage recruitment procedure whereby eligible individuals were randomly assigned only if they

had indicated in a questionnaire that they would be likely to attend screening. "This meant that the compliance rate in the trial was higher than would be expected in a population-based programme, at least in its early years," they write.

In an accompanying commentary, David Ransohoff from the University of North Carolina at Chapel Hill wrote, "The good news is that this size of benefit is large for any cancer screening test, certainly compared with mammography for breast cancer or assay of prostate specific antigen for prostate cancer. On the other hand, a 50% reduction of colorectal cancer incidence (for lesions reached by the scope) is lower than figures popularly quoted for colonoscopy, but on the basis of non-randomised data. Perhaps even greater reduction for screening sigmoidoscopy will be observed after more follow-up."

He added that there remained questions of whether more frequent endoscopy might lead to still greater reductions in colorectal cancer.

■ WS Atkin, R Edwards, I Kralj-Hans et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet* 8 May 2010, 375:1624–1633

■ DF Ransohoff. Can endoscopy protect against colorectal cancer? A RCT. *ibid* pp1582–1584

Single-dose radiation found to be effective for early breast cancer

→ The Lancet

A single dose of radiation administered during surgery was found to be as effective as standard radiation therapy for women with early forms of breast cancer, reports the TARGIT-A study.

Breast-conserving surgery followed by post-operative whole-breast external beam radiotherapy has become the standard of care for many patients with early breast cancer. While radiotherapy is safe and effective and the risk of side-effects is low, many patients find the duration of daily treatments inconvenient. Observational studies and randomised clinical trials have shown that more than 90% of recurrent disease is within the index quadrant, with multifocal or multicentric cancers in other quadrants of breast appearing to remain dormant for many years. This led Jayant Vaidya and colleagues, from University College (London, UK), to the idea that irradiation of the immediate vicinity of the primary tumour might be adequate for achieving local control of cancer.

The TARGIT-A (Targeted Intra-operative radiation therapy) trial, launched in 2000, was designed to determine whether single-dose intraoperative radiation is equivalent to standard external beam radiotherapy using linear accelerators to irradiate the entire breast externally over three to six weeks. The TARGIT approach, pioneered by the UCL group, utilises a device that provides a point source of low energy X-rays positioned in the tumour bed for between 20 and 35 minutes to irradiate tissues at highest risk of local recurrence.

In the study, 2232 women aged 45 years or older with invasive ductal breast carcinoma undergoing breast-conserving surgery were enrolled from 28 centres in nine countries and assigned, in a 1:1 ratio, to receive targeted intraoperative radiotherapy (n=1113) or external beam radiotherapy (n=1119). Neither patients nor investigators were masked to the treatment assignment.

The primary outcome of the study was local cancer recurrence in the conserved breast. At four years there were six local recurrences in the intraoperative radiotherapy group (1.2%) versus five in the external beam radiotherapy group (P=0.41). Complication rates were similar for both groups: 3.3% in the TARGIT group and 3.9% in the external beam radiotherapy group, with the exception that wound seromas needing more than three aspirations were greater in the TARGIT group (2.1% vs 0.8%).

"This large, international randomised trial provides robust and mature evidence that substantiates previous findings showing that targeted intraoperative radiotherapy is safe. Rates of overall complications and major complications were similar in the targeted intraoperative radiotherapy and external beam radiotherapy groups," conclude the authors.

"Our results bring us closer to a scenario in which a patient with early breast cancer might complete all her local treatment, surgical excision, sentinel lymph node biopsy, and radiotherapy at one or two visits, without having to stay overnight in a hospital bed."

Biologically, write the authors, these results challenge two different dogmas. First that whole-breast radiotherapy is necessary in this group of patients and, second, that the traditional radiation dose (much higher than targeted intraoperative radiotherapy) is essential for effective tumour control. "Another interesting biological paradox is that the proportional risk reduction achieved by radiotherapy is the same whether the margins are positive, narrow, or wide," write the authors.

Advantages of intraoperative radiotherapy, they say, include avoiding irradiation of the intrathoracic structures (such as the heart, lungs and oesophagus), reductions in waiting lists for postoperative radiotherapy and cost savings. Longer follow-up is needed to monitor the clinical appearance of new primary tumours outside the index quadrant and delayed recurrences inside the index quadrant.

In an accompanying editorial David Azria and Céline Bourgier, from the Institut Gustave Roussy, in Villejuif, France, write that although the technique has been criticised since it was first developed, due to depth of dose, they are convinced that in elderly patients intraoperative radiotherapy offers "an excellent approach".

"It has been suggested that tamoxifen alone will be sufficient for patients aged 70 years or older. Local or regional recurrences at 5 years were significantly higher in the tamoxifen group than in the tamoxifen plus radiotherapy group. Accelerated partial-breast irradiation is therefore a better alternative than no irradiation at all, and should be widely proposed to these patients," they conclude.

■ J Vaidya, D Joseph, J Tobias et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. *Lancet* 10 July 2010, 376:91–102

■ D Azria, C Bourgier. Partial breast irradiation: a new standard for selected patients. *ibid* pp 71–72

Adopting a child after cancer

The policies, the procedures and the prejudice

For would-be parents rendered infertile by cancer or its treatment, adoption can offer a happy future for them and their child. Some agencies see a cancer survivor as a potential parent with valuable experience of coping with adversity. Others see only an imperfect bill of health, regardless of the prognosis. Be upfront, realistic and persistent is the advice.

➜ Peter McIntyre

The voices seem hardly daring to hope. Carly, newly married when she was diagnosed with ovarian cancer at the age of 33, asks "Adoption after cancer. Is it possible? Is it a dream that I can safely hold onto? I'm not sure."

She feels that the word 'choice' in her life has been redefined. "When I think about our future, a part of me still sees us with a house full of kids, although I question where these kids will come from. After a diagnosis of ovarian cancer I don't know how many adoption agencies are rushing to place a child in your care..."

Previous *Cancer World* articles have followed the journey that women and men who want families make after a diagnosis of cancer, when fertility is affected by the disease or by the treatment.

The emotional wear and tear on a couple or a single women who have been through the cancer journey and then IVF can be overwhelming – what one couple called "an emotional battering".

But some have succeeded in building their family another way, through adoption. Singer songwriter Sheryl Crow was treated for breast cancer in 2006, undergoing surgery followed by radiotherapy. She has since succeeded in adopting twice as a single mother, most recently in June 2010, when Levi James joined the family as a baby brother to Wyatt, who was adopted as a baby three years ago. After adopting Wyatt, she told the media: "He's the first thing I think of in the morning, and the last thing I think of before I go to sleep."

There are many others who would love to start their day, the same way. But would-be parents after cancer also ask themselves, "What will happen to the child if I die?" For prospective adoptive parents this question is still tougher, since the child they adopt has already lost their birth parents and needs security above all.

Victoria, an Italian who has succeeded in adopting after cancer, asked herself this question many times. Like many who have been through the cancer journey, she knows all about the unpredictability of life – but she feels that this also brings a special awareness to being a parent and the care she gives her daughter.

Victoria was diagnosed with breast cancer at the very young age of 24. A few years later, apparently healed, she conceived naturally, without needing

ANNE-MARIE PALMER / ALAMY

fertility treatment. Then, without warning, during the pregnancy her cancer returned, this time with metastases. Victoria faced the choice between starting immediate lifesaving chemotherapy and continuing with her pregnancy.

She says, "The progression of the disease was not compatible with the life of the baby. If I renounced the therapies, it would have been a useless attempt, for me and for the baby. There was no choice. Abortion is a suffering that cannot be explained, maybe one of the worst moments in the life of a woman."

The termination affected Victoria and her husband deeply. But afterwards they talked about the future and decided that they wanted to adopt. They knew that this would not be an easy task but set out on "a bureaucratic pregnancy" with a gestation period of almost three years.

The process involved social workers, psychologists, doctors and judges, as well as medical examinations and psychological tests. Looking back Victoria says, "Some of these people were clever and sensible, but others were stupid and full of prejudice." She felt that some professionals were so insistent that adoptive parents passed every test that "it seemed like a eugenical search for perfection and immortality!"

Then, one Friday, the court told Victoria and her husband that they could become parents to a newborn baby the following Monday. Now Andrea is a cuddly, clever, joyful young child who brought happiness with her. "We thank God every day for having blessed us with Andrea's gift," says Victoria.

She still worries about the cancer coming back, not so much for herself as for her daughter. But she says this is a fear she has learned to cope with. "Everybody can fall ill or even die at any moment in life – the difference being that I am more conscious of that and so may be able to appreciate every single moment of Andrea's extraordinary life!"

Different countries, different policies

The rules of adoption vary between European states and are not part of the EU "acquis communautaire". However under the 1967 European Convention on the Adoption of Children, adoptions are valid only if granted by a "competent authority", which must inquire into the "the

Dare to dream? It's harder to adopt if you have a history of cancer, but some people do succeed, while others find alternative ways to build loving, mutually rewarding relationships with children, for instance through fostering or regular short-break care

"Agencies need to ensure a reasonable expectation of good health at least until the child reaches adulthood"

personality, health and means of the adopter" and his or her ability to bring up the child.

In Germany, the falling birth rate has seen the number of German children being adopted halved since 1994. With 20 applicants for every child it is said to be almost impossible to adopt a German child if you have a serious, potentially life-threatening illness like cancer. Today, in Germany, one-third of children who are adopted come from abroad. Alfred Meyer, chairman of a state-registered adoption placement agency, who specialises in adoptions from abroad, was quoted in *Deutsche Welle* as saying, "Applicants have their homes and bank balances examined. They are subjected to mental and physical checks, and their reasons for wishing to adopt are scrutinised in detail. The whole process takes between one and two years, but even once the applicants have been given the all clear, they have to wait anything up to another two years before they actually have their child."

Inter-country adoption has been widely used by couples in Europe and the USA, especially to adopt babies from China, Eastern Europe and Africa. It has become increasingly controversial, as many children are given up for adoption for reasons of poverty; there have also been a number of scandals, most recently about the alleged abduction of children after the earthquake in Haiti. Recently, Romania, China and several African countries have clamped down on inter-country adoption. According to a policy adopted in China at the end of 2006, consideration as an adoptive parent will not be given to anyone who has "severe diseases that require long term treatment and that affect life expectancy, like malignant tumours…"

Despite restrictions, there are some European countries where adoption is heavily geared towards children from other countries. In Sweden, as recently as 2002, all but 20 of the 1,000 children adopted were from overseas.

There are no data on how many people who have had cancer have adopted. However, demand can be seen by the participation level in the Yahoo group 'Adoption-after-cancer', which has more than 700 members (mainly from the USA) who share experiences, hopes and fears.

One woman who had breast cancer and has now been accepted as an adoptive parent for a baby from her own country reflects on "over 30 agencies called; 15 adoption programs examined; 2 failed attempts at adopting from other countries; a foster care license; any number of dedicated people who believed; and thousands of prayers".

Another writes about how easy it was for her to adopt: "They didn't care at all about a cancer history and 2 weeks ago, we adopted the most beautiful baby boy...we were even in the delivery. It is an open adoption and our birthmother knows I have a history of cancer. … Breast cancer doesn't have to keep you from becoming a mom."

The child comes first

The United Kingdom was one of the first countries in the world to pass legislation on adoption and today has a comprehensive set of procedures that applies equally to children adopted from inside or outside the country. About 3000 children a year are adopted from local authority care and there are around 4000 children in care waiting to be adopted every year.

Child placement consultant Patricia McGinty says that the interests of the child must always come first, but she would not rule out adoption after cancer. Her agency, Be My Parent, is part of the British Association for Adoption & Fostering (BAAF) and identifies possible families for children waiting for adoption and permanent (or long-term) fostering to families, through its specialist newspaper and online service.

"When considering placing a child for adoption, adoption agencies have a duty to consider the needs of the child as paramount," says McGinty. "They have a duty to ensure that adoptive parents will have the physical and mental health to care for the child placed with them, providing them with a

stable, loving home both now and in the future. It is a very important lifelong decision for the rest of the child's life and the rest of the adopter's life. Agencies need to ensure that the adopters have a reasonable expectation of good health at least until the child reaches adulthood.

"Children who need adoptive families have been through a lot. They may have been neglected from early life or experienced the trauma of emotional abuse, physical abuse or sexual abuse. They have had all that to contend with as well as the loss of their birth family and siblings if they have been split up.

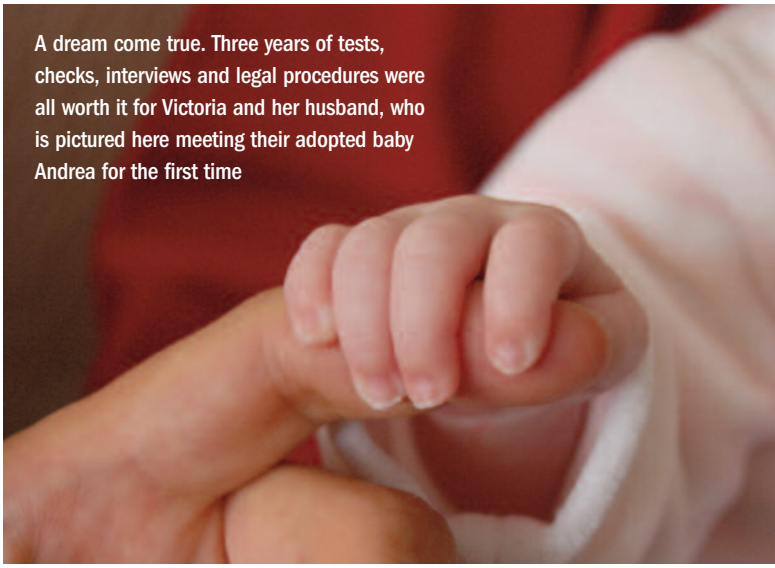
"It is very important that when a child moves on to an adoptive family, they have as much love, attention and stability as possible to help them comes to terms with those difficult experiences. Because of that, the local authority responsible for placing the child will try to minimise any further losses, including the loss of their new parents."

All prospective adopters and foster carers are required to have a medical examination carried out by their GP and the agency may consult specialists about complex medical conditions, like cancer. "The adoption agency may contact the prospective adopter's consultants or oncologist for more information about a prognosis. The final decision regarding approval to adopt would be made by the adoption agency, based on a holistic assessment of the adopter's background and suitability to provide a loving and stable life for a child. Although health is an important consideration, it is not the only factor."

Nothing is set in stone

In practice, someone currently undergoing active treatment would be advised to wait until the treatment was finished, but anyone who has completed treatment and has a good prognosis would be considered. "Nothing is set in stone, and each individual's situation should be considered on its own merits," says McGinty.

"Cancer would not automatically rule anybody out. Everybody will be affected differently by their cancer diagnosis. That is why, if this is known information by the prospective adopters, it is important that they raise this very early on when applying to an adoption agency, so this can be explored."



A dream come true. Three years of tests, checks, interviews and legal procedures were all worth it for Victoria and her husband, who is pictured here meeting their adopted baby Andrea for the first time

Her overall message is to be honest and upfront about your condition, but not to give up hope. "I certainly know professionally and personally some adoptive families where people who had had treatment for cancer have gone on to adopt children. It is not impossible and that would be my encouragement to any prospective adopters where there is a background of cancer treatment. Even if one agency says 'no', it may be worth trying another agency."

British law requires prospective adopters to be assessed (including their health and background status), prepared (learning about the needs of adoptive children) and approved. Statistically, more married couples come forward as adoptive parents. However, single carers can also successfully adopt. Of the 3300 children adopted in England from local authority care in the year to the end of March 2009, 270 children were placed with single people. A good network of relatives and friends, able to provide practical and emotional support is an invaluable

Her overall message is to be honest and upfront about your condition, but not to give up hope

"Any adverse circumstances that they have overcome and learned from are seen as positive experience"

part of life for all types of families, and even more so where a single carer is the main carer. In practice, where one person is affected by a condition such as cancer, adoption agencies may be more likely to consider a couple more favourably when placing a child. However, this is not inflexible.

In Western Europe few healthy white babies are placed for adoption. In the UK, those who are on the waiting list for long periods are likely to be groups of brothers or sisters, where two or more children need to be placed together, children over the age of seven and those from black and ethnic minority backgrounds, particularly children of mixed ethnicity. In addition, disabled children and those whose development is uncertain (perhaps because the mother used drink or drugs during pregnancy) are amongst the hardest to place.

However, it is here that someone who has faced a life-threatening illness and come through lengthy medical treatment may have the most to offer.

Adversity can be a plus

Patricia McGinty says, "We need families who can accept children whose development is uncertain and that could apply to other medical conditions as well. If adopters have undergone adverse circumstances and come out of that positively and can apply it to their parenting, that would be considered a positive. Adoption agencies are not looking for the perfect families. There is a recognition that any adverse circumstances that they have overcome and learned from are seen as positive experience, particularly if that helps them to care more effectively for the child."

The British regulatory system seems to work and many fewer adoptions in Britain are from abroad. McGinty contrasts that with other European countries, including Ireland, where a child usually cannot be adopted without the consent of the birth parents, and as a consequence many children grow up in foster care, while adoptive parents are looking overseas.

Adoption is not the only option. There is in many countries a desperate need for foster parents who can offer maybe short-term care or regular short-break care to help a child remain in their birth family or in their main foster placement. Some of these children may have special needs. This may be a way of developing a relationship with a child and providing them with a close loving and stable experience of family life even if adoption is not possible. In most European countries foster parents also receive some financial support.

Whether it is adoption or fostering, McGinty says, "The important thing is that prospective parents should not automatically give up or rule themselves out. Adoption may not be right for them at this moment in time but something they may be able to consider later depending on the prognosis and their medical situation."

From Italy, the woman who has successfully adopted would echo this. Victoria says that having a child after cancer is part of coming back to life. But she also recognises that "the right of the child to have parents must always prevail over the desire to become parents." If the courts had ruled against them in Italy, Victoria and her husband would have found another way to give their love, perhaps by greater engagement in the voluntary sector.

The story of Victoria's battle with breast cancer and the adoption of her child was published in 2009 in *Ho vinto io*, a compilation of stories from Italian breast cancer patients, edited by M Boldrini et al (2010)

"The important thing is that prospective parents should not automatically rule themselves out"