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Stein Kaasa

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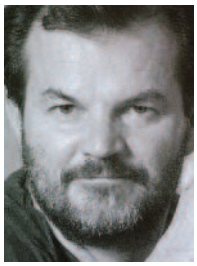

Aspirin for cancer prevention: why wait?

Andrea DeCensi ■ GUEST EDITOR

The prospect is too exciting to dismiss: a single pill – a cheap one too – that, taken regularly, can reduce the risk of not only heart attack, but also developing or dying from several types of cancer.

Evidence that regular use of aspirin can reduce the risk of dying from cancer has been steadily growing. It was boosted last year with publication in the *Lancet*[1] of a meta-analysis of eight trials by Peter Rothwell and colleagues, which showed a substantial reduction in mortality for a number of different cancers.

The study showed that a low dose of aspirin (75 mg per day, or a quarter of the normal dose taken for pain relief), taken for longer than five years, reduces death rates from all cancers by 34%, and for gastrointestinal cancers by as much as 54%.

The risk of death remained 20% lower for all solid cancers over a period of 20 years, with the risk from gastrointestinal cancers dropping by 35% – even though the participants would probably have stopped taking aspirin after the trials ended. The 20-year risk of death was cut by about 30% for lung, 40% for colorectal and 60% for oesophageal cancer.

With data like these, why has no medical organisation issued guidelines or recommendations on the use of aspirin as an anticancer therapy? The problem is that we still lack strong evidence from adequately powered randomised trials. None of the trials included in the meta-analysis was designed specifically to assess whether aspirin reduces cancer incidence or mortality. And although many studies, including a few clinical trials, indicated that aspirin does play a preventive role, other studies have reached a different conclusion. It would take a very long time and a very large study to demonstrate an effect in any trial that took cancer mortality as an endpoint – indeed it may not be possible, particularly as many people are already taking aspirin for cardiac prevention and pain relief.

Potential side-effects have also to be taken into consideration, since aspirin can substantially increase the risk of serious gastrointestinal bleeding, even at low doses.

One issue that needs urgent investigation is the effective dose. Rothwell argues that a daily low dose (such as 75 mg) may be the right choice, while others suggest up to 325 mg at least twice a week. Contributing to the debate is a recent study[2] using aspirin at 300 mg twice a day for two years, in a high-risk population, which cut the rate of colorectal cancer by 63%.

It would be great to be able to say that this century-old pill represents the next great clinical advance in cancer. Yet for the moment, at least, the emergence of aspirin into a cancer prevention role seems to be on hold. The experts are recommending neither for nor against, advising only that any decision about daily aspirin use should be "made only in consultation with your healthcare professional". Posterity will judge whether they are right.

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Stein Kaasa:

let me show you what integrated palliative care can do

Marc Beishon

Patients are falling through gaps in care provision because palliative care is seen as an add-on rather than integral to care plans. So says Stein Kaasa, head of the Cancer Clinic at Trondheim University Hospital. He has convinced his government to take a lead in supporting palliative care, and is busy building a structure for integrated oncology and palliative care that could act as a model for the world.

The World Health Organization has a definition of palliative care, but it is by no means a short one. Yes, it is "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness." But that is just the start. We need to have "early identification and impeccable assessment and treatment of pain and other problems", integration of "psychological and spiritual aspects of patient care", "support systems" for patients and their families, and a "team-based approach".

A crucial part of the definition, as Stein Kaasa, a palliative care expert and head of the Cancer Clinic at Trondheim University Hospital (St Olavs) in Norway affirms, is the last point: "It is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications."

For Kaasa, who has advised the WHO on its cancer work, the definition throws down a challenge to what he calls "mainstream oncology". "Although palliative care, and palliative medicine as it's also termed, has been around for a long time it is still not integrated properly into many cancer departments, which means patients can fall into gaps in their care," he says. The problem, he adds, is that some health professionals – such as cancer doctors and nurses in hospitals – still see it as a specialism that is mainly about taking care of the dying and their families, and they worry that bringing it into the mainstream will mean pursuing futile oncological treatments. "Nurses, especially, may say that palliative care belongs in a nursing home or hospice, and if we

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work there we shouldn't be part of acute medicine."

Kaasa argues the opposite point of view. "Palliative care is important much earlier in the disease trajectory, especially as about 60% of cancer patients receive non-curative care. When you are giving chemo- and radiotherapy as part of life-prolonging treatment – where someone may live two to three years or more – they will have many symptoms and may often need to be supported at home." There is so much new in oncology and in symptom control, says Kaasa, "Patients deserve to have palliative care specialists as part of the oncology team during their cancer journey. I strongly believe that oncology is better if the voice of palliative care is firmly integrated in the healthcare system."

The WHO, he adds, has recently revised its definition of palliative care to include collaboration throughout the care pathway, and integration with oncology where appropriate. Those looking for a model of where that integration is taking place will find one at Trondheim, where Kaasa has also recently established the European Palliative Care Research Centre to drive the evidence base for his speciality.

There are a number of other compelling reasons for bringing palliative care into the mainstream, he notes. They include the best use of expensive treatments in metastatic disease – a huge issue for hard-pressed healthcare systems. Knowledge of metastatic disease itself is an underlying issue, given that it is often the poor relation of efforts put into the curative side of cancer treatment. Palliative care should also be pivotal in bringing together all the parts of healthcare systems and related professions that play a role in caring for cancer patients and their families, whether in the home or in primary care or acute settings. Everything from psycho-oncology to bereavement counselling and

"We know now that we need to start earlier when treating the many people with cachexia"

How are you feeling? Integrated palliative care means not waiting until you have no further anti-cancer therapies to offer before taking steps to improve your patient's quality of life

complementary therapies comes under the umbrella.

Among the general range of side-effects of progressive disease and treatments, two core symptoms stand out which can be extreme for many patients – pain and cachexia (muscle wasting). "In epidemiological studies on pain, about half of cancer patients are not sufficiently treated even when using opioids, and we know now that we need to start earlier when treating the many people with cachexia who have lost a lot of weight and muscle mass," says Kaasa.

As he explains, there is a great deal of research to be carried out on pain and cachexia, as well as on other aspects of palliative care. Such research includes a recent move to investigate biological mechanisms as well as clinical approaches that have been the mainstay. "The problem we have is that in pain, for example, the quality of evidence for management of people with cancer is very low – the studies are poor. There are too many small studies that are inconclusive – they don't have the power we need."

Fragmented research and small studies are common in cancer, he concedes, "but in palliative care it is even more challenging because patients are hard to reach and often very sick, and you need to design studies that can comply with an intervention or medication."

Despite the lack of major studies, the last 10 years have seen a step up in focusing on palliative care and oncology in Europe. This is thanks in part to Kaasa's success in putting the subject on the map in Trondheim when he moved there in 1993, as professor of palliative medicine at the Norwegian University of Science and Technology, which was one of the first such job titles in Europe at the time. He went on to establish a pain and palliative care research group that has carried out and coordinated many studies. "For example, we won an EU grant in the 6th framework programme in 2005 to co-ordinate the European Palliative Care Research Collaborative, under which we ran work packages on understanding and assessing pain and cachexia,

and we also produced European guidelines on managing cachexia and depression."

As always, the issue is the short-term nature of these programmes, and although there are other EU projects underway, Kaasa says that so far there isn't anywhere near the critical mass of support for the wider collaboration and research networks he feels that palliative care needs.

While palliative medicine is by no means just about cancer, it is now such a major part of the speciality that the majority of his own researchers and clinicians in Trondheim are exclusively involved in oncology, as are other units with which they collaborate internationally in countries such as the UK and Canada. The European Association for Palliative Care (EAPC), for which Kaasa is a past president, has a strong oncology track and supported the establishment of the European Palliative Care Research Centre in Trondheim in 2009.

This cancer-only initiative is certainly one of the biggest steps forward recently, but Kaasa says the majority of its funding is from the Norwegian Cancer Society, and from his own hospital as well as the university. Without his vision for palliative care in oncology and the backing of Norway's advocacy groups this centre would not be up and running, although it is attracting various grants from the EU and other sources, and of course enjoys the support of the EAPC and international colleagues.

Given his achievements so far, Kaasa is now aiming high at Trondheim – "I want to build a structure for integrated oncology and palliative care that will be a window for the world that will show what can be done," he says. It's an ambitious goal for what is a northern outpost in Europe, but as he says, he has already fought and won the battles to prove the need for integration locally, and with long-standing expertise in international networking there is every chance that he will ensure that Trondheim will be seen as the global model he envisions.

Kaasa was a national cross-country skiing champion when at high school in Norway, and gained a great start for his early career when he landed a sports skiing scholarship at Denver University in the United States, where he was also able to model his own 'pre-med' course in anticipation of a return to Norway. Then in Oslo, he completed his medical training, taking in surgery, internal medicine and family practice. The latter was a career option until, unsure of what direction to take, he contacted Herman Høst, the 'father' of Norwegian oncology, and gained a short-term post at Oslo's Radiumhospital.

"There I was challenged by a senior lecturer to look at lung cancer patients and the use of cisplatin in people with a short life expectancy, and I worked on a randomised trial between chemo- and radiotherapy, which was the basis of my PhD thesis. We were one of the first to actually ask people how they felt during their treatment – what we now call patient-reported outcomes – and our group was one of the movers in the development of the QLQ-C30 questionnaire at the EORTC for assessing the quality of life of cancer patients."

It was the opportunity to do this kind of research that quickly convinced Kaasa that his career lay in oncology and not as a family doctor. He then gained his oncology board certification working on the spectrum of cancer issues at the Radiumhospital and, like oncologists in certain countries such as the UK and other Nordic countries, Kaasa is certified in both chemo- and radiotherapy, as a clinical oncologist. But his academic focus was on the non-curative side – and he duly completed a PhD on quality of life and survival.

"Although palliative care had been developed primarily in the UK back in the 1960s, thanks to the hospice movement, it was mainly outside of mainstream healthcare. In hospital oncology it hasn't really taken off until recently," says Kaasa. "That's because in the late 1980s we had a strong belief that we would see the sort of major improvements in cure rates that we had seen with testicular cancer and lymphoma, for example. When I was working on lung cancers we really thought we would cure them with high-dose chemotherapy and bone marrow transplants."

"I want to build a structure for integrated oncology and palliative care that will show the world what can be done"

Recent years have seen a repeat of this belief, he says, as the new targeted therapies have again pushed back palliative care to some extent, fuelled by the huge promotional activity of the pharmaceutical industry – although he adds that pharma was the first in offering support for quality of life studies when he was starting out. "Companies realised it was important to document subjective factors as well as response rate," he says.

After establishing himself as a consultant oncologist in Oslo, the opening for the palliative medicine professorship in Trondheim came up. "In Norway we had been debating what we should do about palliative care and it was again the Norwegian Cancer Society that was instrumental in putting out a bid to set up a programme at one of our university hospitals. Trondheim won and I was asked to apply."

Although Kaasa enjoyed the support of the hospital's oncology department and the head of nursing, he still encountered most of the objections about actually integrating palliative care. "I won the battle by bringing in the academic side and starting a research programme, and putting a lot of energy into international collaboration and leadership. It's hard for opponents to criticise solid research – especially as, after seven years or so, we were producing as much as 80% of the publications from the Cancer Clinic."

Kaasa also argued from a clinical perspective that patients suffering, for instance, from pain with bone metastases needed to be treated with radiotherapy, and that to carry out academic medicine properly on such approaches palliative care had to be applied early in the journey rather than waiting for oncologists to deliver patients to palliative care professionals in another location.

From humble beginnings – when he started Kaasa had just one other doctor and two nurses – the palliative care team in Trondheim is now almost 30 strong, with molecular biologists and social scientists, more than 20 PhD students, a number of international researchers and visiting professorial placements, and various clinical and research input from other specialists in the university hospital, such as pain specialists.

Kaasa was asked to head the entire Cancer Clinic in 2010, and so is in the ideal position to oversee the integration he promotes. "And that's what you would see is different here – palliative care doctors at our morning case meetings, which we hold every day. I don't see patients myself now but I do become involved in particularly challenging cases."

An early randomised study comparing specialist palliative care with care as usual, published in the *Lancet*, played a critical role in setting the agenda, says Kaasa. One major finding was that patients in the intervention group benefited from an integrated pathway by being able to stay longer at home. "An interesting spinoff was that the families reported better health even one year after the patient had died," he says. Trondheim has now produced hundreds of studies related to palliative care, many of them in top-rated journals, according to Kaasa. Other studies have focused particularly on treatments, finding benefits for example in reducing the number of radiation fractions that need to be given to treat lung cancers and bone metastases, saving much trouble for patients and also costs.

Current research priorities for the field are revealed in a pan-European survey under an EU 7th framework programme project called PRISMA, which shows that the top topics are pain, assessment tools, quality of death and last days of life, fatigue and cachexia, and family and carers. The main barriers are, inevitably, lack of funding, time, expertise and personnel.

Pain is still a major problem, says Kaasa. One reason he cites is that many patients are not diagnosed and followed-up appropriately. Another is that they do not receive effective treatments because they fall into gaps – a hospice physician may have no access to radiotherapy to treat bone metastases, while a radiotherapist may not know enough about opioids. "Optimal pain control needs a combined approach, including specialists at pain clinics. We have a close relationship with our pain

"An interesting spinoff was that the families reported better health even one year after the patient had died"

clinic in Trondheim – but there can be little such collaboration between pain specialists and palliative care around Europe, as the pain clinics deal mainly with non-malignant conditions. We also have a growing population of cancer survivors who suffer non-malignant pain from side-effects later in life. We have to collaborate more for patients."

One urgent need is to establish a consensus on pain assessment tools in palliative care and to update guidelines based on much stronger evidence. Kaasa points to some progress here: a recent special issue of *Palliative Medicine* (July 2011) published updated pain guidelines from the EAPC, the evidence base for a set of review articles, and there is now a much better platform on which to build cancer pain research.

Kaasa's group is the leader of the European Pain Opioid Study (EPOS), which is a translational research project looking at the biological action of the drug. A major change in recent years, he notes, is a move to joining forces with basic scientists to research the biology of late-stage disease and effects, in addition to the patient-reported clinical studies.

"We have also been researching the genetic basis of pain to see if we could find a biomarker for pain response, but we had a negative result, which is still important to publish. We have been critical of the methodology often used in this type of research – those who go on 'fishing trips' for single-nucleotide polymorphisms to find such biomarkers in clinical medicine, when there are so very few in use in oncology. But we have more encouraging signs for our work in cachexia." (See also box).

One aspect of his field particularly annoys Kaasa, and that is terminology. As far as he is concerned, it is called 'palliative care' or 'palliative medicine' and should cover the vast majority of the advanced cancer journey. But he says confusion can be spread by the use of 'end of life care' and 'supportive care'. "In some cancer centres this is often about competing for resources, with some focusing on what they call earlier symptom control in 'supportive care', while leaving others to do the 'end of life'. Yes, if you have a large palliative care team you can have people focusing more on early symptoms, but really this is often about a resources battle and not integrated care, and of course again it is the patients who fall into the gaps."

A powerful way to get the message across about palliative care, he believes, is to have many more doctors gaining a palliative medicine qualification as an addition to their main work. "We now have a two-year course in the Nordic countries that we started in 2003, and it was officially endorsed, recently, for any doctor to study palliative medicine during their normal job, although they do have to take about six weeks out to attend the various modules, which are run at various locations in Scandinavia." The Nordic Specialist Course in Palliative Medicine, as it's called, is based on the British curriculum in palliative medicine, which is a standard for many countries.

There's a big difference though between Britain and Norway when it comes to full-time palliative care practitioners, says Kaasa. "In Britain you can train from the start as a palliative medicine specialist, but here you need to have another speciality, such as oncology, first – all the palliative doctors in my unit are also oncologists." In fact, one other issue he had to deal with on taking up his professorship at Trondheim was that his department was expected

CACHEXIA: EXPANDING THE EVIDENCE BASE

Cachexia is primarily seen in patients with advanced disease, but it may also be a symptom of those undergoing curative treatment, says Kaasa. At present, there are limited ways to manage the condition, partly because there has been a big knowledge gap about its assessment. But that gap has now been addressed, according to current evidence, in a consensus paper on the definition and classification of cachexia by Kaasa and international colleagues, led by Kenneth Fearon in Edinburgh and Florian Strasser in St Gallen (*Lancet Oncology* 2011, 12:489–495).

As the paper makes clear, cachexia is a challenging syndrome, with complex interplay between reduced food intake and abnormal metabolism, where loss of muscle is the key impairment. The new consensus tries to define the stages of cachexia and which features to assess, including early identification of symptoms that could lead to better interventions.

Kaasa says there is promising molecular biology and genetic research that may provide more answers. Meanwhile, based on clues of what drives the inflammation and catabolism behind the condition, his group, with colleagues in Canada and the UK, has designed a randomised phase II study looking at a composite treatment of anti-inflammatory drugs, nutrition (where fatty acids may play a preventive role) and physical exercise.

"This is a pragmatic study, as the research on cellular mechanisms will take years," he says.

Issues surrounding the psychological impact of cachexia on patients and those caring for them were explored in a Patient Voice article published in *Cancer World* March/April 2009

to handle conditions other than cancer, such as coronary heart disease and neurological illnesses.

"But to work in specialist palliative care you have to know the disease you are working with, in my view. After 10 years or so we stopped everything except oncology." A cardiologist with a palliative medicine qualification is much better placed to work with heart patients, he says. "But outside the hospital a GP with palliative care knowledge can see everyone."

An early success in clinical care in Trondheim was being allowed to involve multidisciplinary teams in seeing patients at home, and not just as in- and outpatients, which was a start in widening the care pathway. "There was no reimbursement system for visiting patients outside the hospital and so we went to the health authority and were granted a special arrangement – financial incentives can be very powerful in changing practice, I feel."

Since then he has helped promote a palliative care strategy that works across all levels of healthcare, and which has been part of Norway's cancer plan. Notable steps have been establishing service development units in each health region, encouraging more hospital directors to set up palliative care units, and making better provision for specialist beds in nursing homes. In 2004, a Norwegian standard for palliative care was published.

Kaasa has also made his mark in Norway in strategies for the wider healthcare system and the country's cancer plan – among his many posts he is currently the national cancer director. He stresses how crucial it is to develop evidence-based guidelines in healthcare – guideline work has been among the more successful parts of Norway's cancer plan. What many other countries lack, in his view, is the kind of palliative care model that Norway now has.

The EAPC, with partner organisations such as the International Association for Hospice and Palliative Care (IAHPC) and the Worldwide Palliative Care Alliance (WPCA), has set out a framework for development (the so-called Budapest commitments), which is an initiative aimed at national associations and includes defining standards of care. An EU 7th framework project, IMPACT (implementation of quality indicators in palliative care study), is looking at cancer and dementia care with work packages on organisation and implementation of care (see www.impactpalliativecare.eu).

These are good steps, says Kaasa, but Europe is some way from widespread quality-audited palliative care in a majority of oncology departments. He would like to see the EAPC gain funding to produce an oncology training curriculum, for palliative care to get a seat at the top table in ECCO, and for the subject to be addressed better at general cancer conferences, where it is often a side session that is not well attended. ESMO, the European Society for Medical Oncology, to which he belongs, could do much more on palliative care, he feels; in contrast, EONS, the nursing society "is much more supportive." Next June, Trondheim is hosting EAPC's 7th world research congress, which will be an ideal place to hear the issues first hand.

Again he mentions the value of politicians setting economic incentives to drive change, and Trondheim's Cancer Clinic is an example of what can be achieved with integration – the number of beds has been cut from 68 to 36 following success in managing more cancer cases as outpatients – a caseload that is rising of course. "Metastatic disease incidence will increase 2% a year up to 2020," he says.

Not least of the issues is the cost of treatments in people with advanced disease, which Kaasa has also been advising the Norwegian authorities about. "We are seeing debates now about the cost–benefits of modern oncology even in the US – 10 years ago, the drug budget at our department in Trondheim was a tenth or so of what it is now." He mentions a recent US study that randomised palliative care against mainstream oncology early in lung cancer. It found the intervention group lived longer and had fewer depressive symptoms, while the

"To work in specialist palliative care you have to know the disease you are working with"

The palliative care group lived longer, while the control group received more chemotherapy

control group received more chemotherapy (*NEJM* 2010, 363:733–742).

Naturally, he may not be the most popular person with pharmaceutical companies, given his insistence for his team to use evidence-based approaches where possible even in advanced disease. "I've been in oncology a long time and I can see no major breakthroughs and just that growing metastatic burden." He adds though that he is of course interested in promising drugs, and also in new uses, such as investigating how chemotherapy can be used to treat pain and other symptoms – an under-researched field.

There is still a pioneering air about palliative care in oncology given the major multidisciplinary research agenda still ahead, and indeed in the US a recent spate of articles in the mainstream media have just 'discovered' the speciality as an evidence-based way to approach care for terminally ill patients, for whom futile treatment is common – countering the right-wing's insistence that discussing end-of-life options will lead to rationing and bureaucratic 'death panels'. Kaasa says Europe is ahead in models of palliative care, thanks to pioneers such as the UK's Geoff Hanks, who was one of the founders of the EAPC, an advisor to the European Palliative Care Research Centre and a mentor when Kaasa was venturing into the field. "It was controversial when I started to focus on quality of life at the Radiumhospital, and I did push palliative care perhaps too strongly in the early years – but I think I was right," he says.

Kaasa has four children and has remarried, to Anne Kari Knudsen, a pain researcher in his department. Skiing and fitness still play a big part in his routine.

"My aim now is to help establish a sustainable network of international centres conducting large-scale research on palliative care in cancer, and in particular I want to gain new insights into pain and cachexia. I won't stop pushing too for even better integration in Norway's healthcare system. And I'll stay here in Trondheim – the skiing's better."

Quality of life. With daughter Karen Johanne at their summer cabin in Risør

Optimising dose-dense regimens for early breast cancer

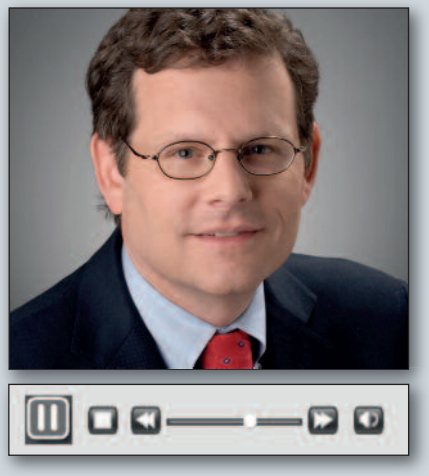
Dose-dense regimens are intended to increase efficacy, not by increasing the patient's total exposure to a drug, but by decreasing the time between doses. Does it work? And what happens to toxicity, especially where targeted agents are added? Clifford Hudis takes a look at the evidence in early breast cancer.

Why escalate the dose of cancer therapies? The rationale is that escalating the dose should kill more cancer cells. This has been seen many times in preclinical models in laboratory experiments and sometimes in the clinic, but not consistently. For example, two large, randomised trials, including a total of nearly five thousand patients in the NSABP (National Surgical Adjuvant Breast and Bowel Project) in the US showed no effect of escalated doses of cyclophosphamide on outcomes. These trials tested five dose levels, where the dose was doubled in dose size, doubled in dose exposure, doubled in dose size again, and doubled in total exposure again, so that doses ranged from 600 mg/m^2 every three weeks to four times greater (see figure, p14 *top*). Results showed no impact on either disease-free or overall survival across these two sequential studies.

Previous results, such as those from Budman et al. (CALGB 8541) suggest that there could be a dose–response relationship for cyclophosphamide, but only at lower doses; the NSABP data show that this does not

European School of Oncology
e-grandround

The European School of Oncology presents weekly e-grandrounds which offer participants the opportunity to discuss a range of cutting-edge issues, from controversial areas and the latest scientific developments to challenging clinical cases, with leading European experts in the field. One of these is selected for publication in each issue of *Cancer World*. In this issue, Clifford Hudis, from Memorial Sloan-Kettering Cancer Center, New York, provides an update on optimising dose-dense regimens for women with early breast cancer. This is based on a News and Views article in *Nature Reviews Clinical Oncology* (2010, 7:678–679). Fatima Cardoso, from Champalimaud Cancer Centre, in Lisbon, Portugal,



poses questions arising during the e-grandround live presentation. It as 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

continue at higher doses. We have seen similar results for anthracyclines and taxanes and most other chemotherapy drugs.

In optimising chemotherapy regimens with regard to dose and schedule, there are essentially two aspects to consider. On the one hand there is the Gompertzian growth kinetics of breast cancer cells, as is true for all other solid tumours, and indeed all cell and tissue types. The tumour, while always growing, appears to have a decreasing rate of growth over time. This is not actually true when you look at raw numbers, but it is true when you look at volumes. That is because of the effect of three dimensions in minimising the perception of volume change. It is also a reflection of the balance (or imbalance) between cell division and cell death as it changes with tumour growth, perhaps due to alterations in the delivery of nutrients and other factors.

If we administer chemotherapy based on the Skipper–Schabel model (see figure, *bottom right*), the green arrows indicate the further reduction with each dose of chemotherapy, which we have always been taught is a log kill effect. The black arrows show the result of shortening the time between treatments on the log kill effect, which is what we call dose density. More frequent (dense) dosing decreases the time for tumour regrowth in between doses. It allows for the treatment each successive time of an ever smaller volume of tumour and that, in turn, results in a greater overall cell-kill.

Is the log cell-kill model reflected in the clinic?

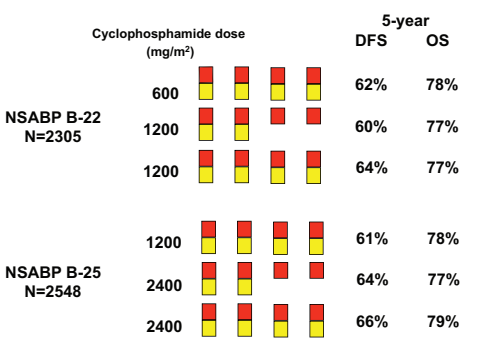
A study from Milan (see p15 *top*) explored sequential or alternating treatment with CMF (cyclophosphamide, methotrexate, 5-fluorouracil) (in yellow) and doxorubicin (in red). The theory was that alternating these non-cross-resistant treatments would yield greater cell-kill. That is the arm represented by the top row of the figure. As a control, they administered the same four doses of the doxorubicin first, followed by the same total eight doses of CMF sequentially. Over the nine months of treatment, every patient on this study received the same four drugs, CMF and doxorubicin, with the same size doses of each drug and the same total dose of each drug. This emerges as an elegant test of dose density. The results speak for themselves, favouring the dose-dense regimen.

Janice Gabrilove and colleagues, at my institution, first used growth factors – specifically granulocyte colony-stimulating factor (G-CSF), also known as filgrastim – to reduce neutropenia and associated morbidity due to chemotherapy in patients with bladder cancer. Although they gave full chemotherapy at a standard interval, all of the patients (100%) had full recovery of blood counts by day 14, and would have been able to receive planned chemotherapy, compared to only 29% of those not given G-CSF (*NEJM* 1988; 318:1414–22). As investigators were beginning to explore significant dose escalation, based on the hypothesis that the dose-response relationship was linear, we instead went in a different direction and began to explore dose density, meaning shortening of the intervals between treatments.

The figure on page 15 (*bottom*) summarises three sequential pilot studies at the Memorial Sloan-Kettering Cancer Center (MSKCC). First, we were able to give high-dose cyclophosphamide (a very high dose of 3.0 g/m^2) at two-week intervals with growth factor support. The second study added paclitaxel, in one of the first trials to add this, or any, taxane as adjuvant therapy (the ATC regimen – **A**driamycin (doxorubicin), **T**axol (paclitaxel), **C**yclophosphamide). In this study the dose interval for doxorubicin was shortened – we gave three doses of each of the three drugs, all at two-week intervals and demonstrated feasibility, albeit with significant toxicities attributable to the use of higher doses of the individual agents than are currently employed.

Later, in a third study, we randomised

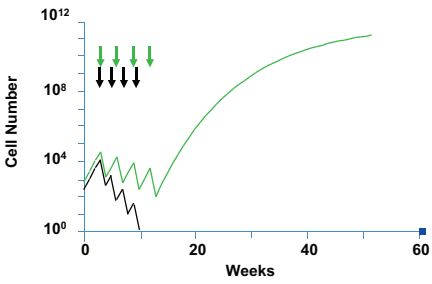
CYCLOPHOSPHAMIDE DOSE ESCALATION



Increasing the total amount of cyclophosphamide used in adjuvant treatment from 600 mg/m^2 to four times that amount had no effect on outcomes in these two large NSABP trials

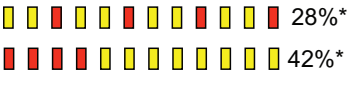
Sources: BS Fisher et al. (1997) *JCO* 15:1858–69; BS Fisher et al. (1999) *JCO* 17:3374–88

IMPACT OF MORE FREQUENT DOSING



A prediction of the Skipper–Schabel model of log cell-kill is that more frequent (denser) dosing gives the remaining cells less time to regrow between doses, allowing treatment of a smaller volume, which then results in greater overall cell-kill

SEQUENTIAL OR ALTERNATING AGENTS



By showing that alternating non-cross-resistant treatments gave inferior results than using them sequentially, this Milan trial provided evidence to support the principal of denser dosing

Source: G Bonadonna et al. (1995) *JAMA* 273 :542–547

patients to concurrent or sequential therapy with paclitaxel and cyclophosphamide, but all drugs were given in a dose-dense regimen. This study demonstrated that with these high doses, the concurrent regimen was no better in terms of toxicity. These studies were all too small (or non-randomised) to allow for efficacy comparisons.

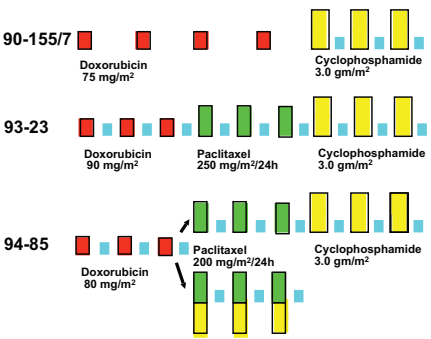
As one considers the results of trials that employ dose-dense regimens, it is important to be wary of possible confounders that can compromise the interpretation of such studies. For example, while we can achieve a dose-dense regimen with short intervals, testing it requires carefully controlled studies. Comparing four cycles of low-dose versus high-dose chemotherapy tests dose size. Comparing four cycles of a drug versus six cycles of the same size dose tests number of doses, and also tests total drug exposure, but not density. Controlling dose size but changing the frequency of administration – or density – while controlling the total dose number, is a pure test of dose density.

A typical design – and I have taken part in these studies myself – is four cycles of low-dose chemotherapy over three-week intervals, compared to three cycles of higher-dose every two weeks. This changes several parameters so it is not always clear what is being tested.

One example of a positive study was the AGO (Arbeitsgemeinschaft Gynaekologische Onkologie) trial (see p16, *top*). Here, a dose-dense regimen of epirubicin, paclitaxel and cyclophosphamide (ETC), given with growth factor support, was superior in long-term follow-up to the conventional epirubicin/cyclophosphamide (EC) paclitaxel regimen (*JCO* 2004, 22:6s, abstr 513). However, the number of doses of the three drugs varies and the size of the doses varies, as well as the dosing interval. Hence, while this study clearly demonstrated the superiority of a dose-dense regimen, critics could claim that this was due to other factors, such as the larger doses of the individual drugs.

Weekly paclitaxel has been called "dose-dense" by us and others. However, here again there can be confusion

MSKCC DOSE-DENSE PILOT TRIALS



These early trials conducted at Memorial Sloan-Kettering Cancer Center tested the feasibility of increasing the frequency of dosing in terms of toxicity (numbers down the left-hand side indicate the year of the trial followed by its serial number)

in terms of what is tested in clinical trials. In the ECOG 1199 (Eastern Cooperative Oncology Group) study, AC was given at three-week intervals, followed by one of two taxanes – paclitaxel or docetaxel – using one of two schedules: weekly or three-weekly (q3). Weekly paclitaxel appeared to be superior to q3 paclitaxel. However, we note that 80 mg/m² weekly of paclitaxel for 12 weeks is not the same as 175 mg/m² q3, and so there are multiple variables at work here: dose number, dose size and frequency of administration.

The Cancer and Leukemia Group B dose-density trial CALGB 97-41 also employed a factorial design (see p 16, *bottom*). We asked two questions: the first question was about the frequency of administration, comparing q2 therapy with G-CSF support to q3; the second compared concurrent AC therapy with sequential therapy. What makes this study interpretable for us is that every patient had the same four doses of the same three drugs. All that varies across the four treatment assignments is concurrent or sequential dosing, and dose density.

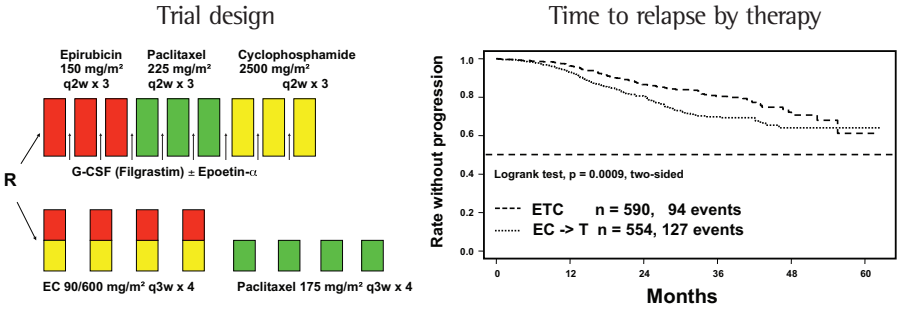
Results show that q2 therapy was superior to q3 for disease-free survival; this was also true for overall survival. There was no difference between sequential and concurrent therapy. We continue to use concurrent therapy most of the time because it allows us to get the treatment completed faster. But that is not the same as saying it is better, other than in terms of convenience.

Toxicity

Once one accepts the superior efficacy of dose-dense treatment, the next concern is toxicity. This has become a particular issue in an era of trastuzumab and HER2-directed therapies for patients with HER2-positive disease.

The cardiotoxicity results from CALGB 97-41 showed the only acute cardiac event occurred in the patient

THE AGO TRIAL: ETC VS EC→T IN PATIENTS WITH 4+ LYMPH NODES



The more dose-dense regimen, which also included higher dose levels, gave superior results in the study by the German Arbeitsgemeinschaft Gynaekologische Onkologie

q2w, q3w – every two weeks, every three weeks. *Source:* VJ Möbus et al. (2004) *JCO* 22:6s, abstr 513

you would have least expected: one treated with q3 single-agent doxorubicin. Looking at the total number of cardiac events – although this was purely exploratory and done retrospectively – showed that numerically there were twice as many events with q3 therapy as with q2 (2.5% vs 1.5%). This gave us some comfort that dose-dense therapy does not raise the risk of cardiac toxicity compared to q3.

This allowed us to go forward with pilot studies of dose-dense therapy and trastuzumab and also bevacizumab. The tables opposite show three studies of dose-dense AC with targeted therapy done by our group at MSKCC, and colleagues at the University of California San Francisco (UCSF), and the Dana-Farber Cancer Institute. The right-hand table summarises the cardiac toxicities, showing essentially no signal of acute cardiac toxicity over the four doses of AC across the several hundred patients.

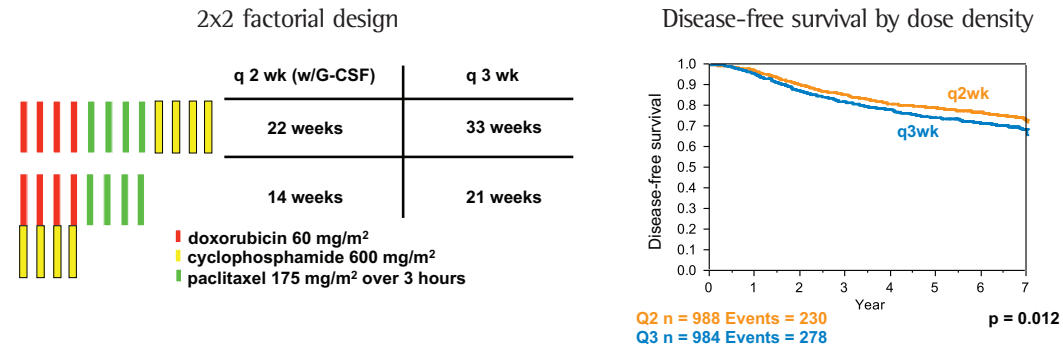
Longer term follow-up does not show any clear signal that dose density represents a special challenge for the delivery of full doses and durations of these regimens (*JCO* 2009, 27:6117–23). For comparison, in the cooperative group trials, about 65% of patients finished their full year of trastuzumab, whereas this number was about 80% in our studies.

TAKING DOSE-DENSE THERAPY FORWARD

We incorporated the results of CALGB 97-41 into CALGB 40101. Initially this was a study of weekly paclitaxel for 12 or 18 weeks, versus AC q3 for four or six cycles with G-CSF. It was a two-by-two factorial design, comparing AC against single-agent paclitaxel for low-risk breast cancer. It was also a comparison of a longer therapy (six months) versus shorter (four months). There were those who argued that the superiority of AC followed by paclitaxel (or docetaxel) was not really attributable to taxanes per se but instead to the eight cycles of treatment which were presumed to be superior to four. Others have argued that six cycles of AC-containing therapy is better than four.

Based on the results of CALGB 97-41 we were motivated to change the study. With fewer than six hundred patients recruited, we modified it to include dose-dense therapy (q2 administration) and six cycles versus four. We continued the AC versus paclitaxel randomisation. In a still later modification of the study we dropped the six versus

CALGB 97-41 INTERGROUP NODE+ TRIAL



The more dense dose (q2) gave better results in both the sequential and the concurrent regimens

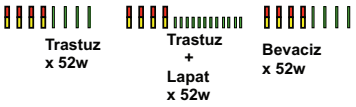
q2wk, q3wk – every two weeks, every three weeks; G-CSF – granulocyte colony-stimulating factor

Source: M Citron et al. (2003) *JCO* 21:1431–39

TARGETED AGENTS WITH DOSE-DENSE AC: TOO TOXIC?

Three MSKCC studies

	AC-PT	AC-PT L	AC + nab-PB	Overall
n	70	95	80	245
Med Age	49	46	48	47
Range	27-72	28-73	27-75	27-75



Three studies conducted at Memorial Sloan-Kettering Cancer Center showed that dose-dense AC (doxorubicin+cyclophosphamide) can safely be used even with targeted therapies that are associated with cardiac toxicity, such as trastuzumab (T), lapatinib (L) and bevacizumab (B)

Cardiac safety with bevacizumab (B)

	All Patients	ddAC alone	ddAC + B
Total patients	182	104	78
Baseline LVEF	68% (53-82%)	69% (54-81%)	68% (53-82%)
Post ddAC	68% (52-81%)	68% (52-81%)	68% (53-77%)
LVEF ↓ to <50%	0	0	0
Sx'ic CHF	0	0	0
Change in LVEF			
↓ >15%	1 (0.5%)	0	1 (1.3%)
↓ 10-15%	6 (3.3%)	2 (1.9%)	4 (5.1%)
↓ 5-9%	28 (15.4%)	19 (18.3%)	9 (11.5%)
↓ <5%	48 (26.4%)	27 (26.0%)	21 (26.9%)

P – paclitaxel; dd – dose-dense; LVEF – left ventricular ejection fraction; Sx'ic CHF – symptomatic congestive heart failure. *Source:* PG Morris et al. (2009) *JCO* 27:6117–23

four cycle randomisation, making it a simple two-way comparison of paclitaxel versus AC, each then only administered for four cycles.

Results reported by Larry Shulman at San Antonio (2010) showed recurrence-free survival and overall survival with four cycles of treatment versus six were indistinguishable. We do not yet have the results of the AC versus paclitaxel comparison, but our data and safety monitoring board confirmed that they do not confound our results.

Is there a better AC or paclitaxel schedule?

SWOG study S0221 used a two-by-two factorial design of six cycles of dose-dense AC compared to a regimen of low-dose weekly doxorubicin regimen along with oral daily cyclophosphamide. Apart from that randomised comparison, they compared q2 paclitaxel for six cycles versus low-dose weekly paclitaxel for 12 weeks. Recently, they dropped the AC portion of the randomisation and shortened it to four cycles of every other week dosing. This was based on a futility analysis that weekly doxorubicin and oral cyclophosphamide could never be superior to the six cycles of AC. It does not mean it is worse. Hence the simplified design is now four doses of q2 AC, and the taxane comparison of low-dose weekly paclitaxel versus higher-dose q2 continues.

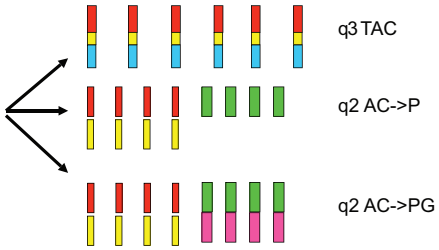
The NSAPB B-38 trial (see p 18, *top*) compares dose-dense AC paclitaxel (*middle row*) with TAC (*top row* – **T**axotere [docetaxel], **A**driamycin [doxorubicin], **C**yclophosphamide) and experimental therapy of dose-dense AC paclitaxel with gemcitabine (*bottom row*). The tAnGo study, a UK-based trial that looked at the potential benefits of adding gemcitabine to an anthracycline- and taxane-containing adjuvant treatment regimen in early breast cancer, was negative. This suggests that the notion that gemcitabine as a fourth chemotherapy drug is going to add to this cohort of patients is unlikely to be supported.

Can we further decrease intervals and increase dose density?

The ECOG 5103 bevacizumab trial is comparing AC, followed by weekly paclitaxel alone, with AC plus bevacizumab followed by paclitaxel plus bevacizumab, or AC followed by paclitaxel, both with bevacizumab and then followed by bevacizumab (see p 18, *bottom*). If bevacizumab adds a benefit, this study also allows us to ask about the duration of its use. Because clinicians have different views on the appropriateness of dose-dense therapy, the dose-dense regimen is allowed, as is q3 administration, and the patients were simply stratified on that basis.

Our group has gone ahead asking whether we can push this further. The first pilot study, conducted by Monica

NSAPB B-38 THREE-WAY STUDY



This study aims to find out whether dose-dense doxorubicin+cyclophosphamide (AC) followed by paclitaxel with or without gemcitabine gives better results than three-weekly docetaxel+doxorubicin+cyclophosphamide (TAC)

Fornier, looked at 10- to 11-day intervals with sequential EC and paclitaxel using conventional G-CSF, because you cannot use pegylated G-CSF with such a short interval. The study demonstrated that this was feasible, but a randomised trial would be needed to show efficacy.

We then turned our attention to intravenous CMF, which was given two weeks on and two weeks off in the Milan studies in the past. Here we gave it every 14 days without breaks, which modelled the dose-dense experience of the CALGB. All we wanted to demonstrate was that it was feasible, because there are clinical reasons, from time to time in individual patients, to try to accelerate CMF, and when we treat patients in the low-risk setting this can be a viable alternative. For this not to be justifiable, we would have to show that shortening the interval makes the therapy less effective, but we have never seen evidence of that. Feasibility was strained at intervals of 10–11 days but not at 14 days.

Dose-dense treatment in the palliative setting

Typically, we do not do studies of dose density in the palliative setting, because our goal here is not necessarily to achieve the highest response rate, or quickly deliver the lifetime tolerable (cardiac safe) dose of AC when it is used for palliation. Instead, our goal is to use the least toxic therapy that we can.

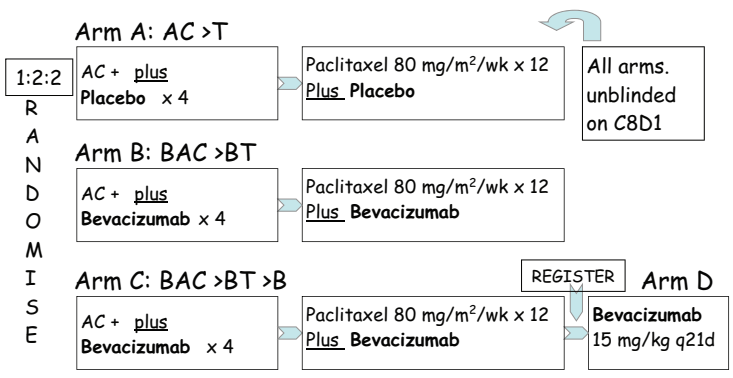
Capecitabine has high efficacy but also toxicity; giving the drug continuously for 14 days on a 21-day cycle results in a high rate of diarrhoea and gastrointestinal distress in the second week. We looked at mouse models of a capecitabine-sensitive tumour cell line. The maximal impact of therapy occurred eight days after starting treatment. This means that each day after that time point, if we continued to dose with capecitabine, cell-kill still occurred but it was less than the day before. The downside is that the toxicities accumulate so a week off is still needed to recover. We modelled the impact of a dose-dense schedule, which consists of one week on and one week off and this predicted that stopping therapy earlier, at one week, would allow for the earlier imposition of the needed seven-day break, but then an earlier re-initiation of treatment with resumption of greater cell-kill.

In the clinical extension of this work, our phase I study showed that this was feasible, and we have now done phase II studies with weekly (one week on, one week off) capecitabine combined with lapatinib or with bevacizumab, all of which have been feasible. This schedule has been widely adopted by clinicians because, as a practical matter, they so often have to stop before 14 days because of toxicity. This is a demonstration of the way in which a dose-dense schedule can be advantageous in the palliative setting as well as more curative in the adjuvant setting.

Conclusion

Dose scheduling – specifically in terms of density – is important, and it should be maintained in the adjuvant setting for both efficacy and toxicity. For example, using growth factor support with dose-dense AC not only

ECOG 5103



This study is looking at the impact of adding various schedules of bevacizumab to an AC → T regimen; investigators can choose between standard (three-weekly) or dose-dense (two-weekly) AC dose frequency

C8D1 – cycle 8 day 1

enhances efficacy but also halves the hospitalisation rate (typically due to neutropenic fever). At the same time, it is fair to say that the cost issue is not fully addressed. Growth factor support is not inexpensive and the cost varies widely, making it unlikely that we will ever be able to develop an absolute answer on this issue. Cost-effectiveness in the curative setting depends, in part, on how much value is put on lives saved.

Finally, supportive care, in the form of growth factor use, is what facilitates the improved chemotherapy effect, so that is a critical part of the story. As we move further into the era of molecularly targeted therapies, it is important to note that dose-dense therapy does not preclude, and in fact supports, the use of these agents.

Q&A

Fatima Cardoso (FC) from the Champalimaud Cancer Centre, in Lisbon, Portugal, hosted a question and answer session with Clifford Hudis (CH)

Q: *[Ukraine]: In your opinion, should we use metronomic chemotherapy or dose-dense chemotherapy? Which of the two will be the preferred option for the future?*

CH: A metronome is, of course, the device that we use in piano lessons to keep time. The term is now being used, typically, to refer to low-dose weekly therapy, but essentially every regimen we ever use matches the metronome, with regular cycling of therapy. I reviewed a couple of studies with cyclophosphamide, doxorubicin and paclitaxel that directly answer the question on low-dose weekly therapy. Perhaps the best was a SWOG study with low-dose, weekly doxorubicin with oral daily cyclophosphamide compared to dose-dense AC, showing it was not better but somewhat more toxic. A study with low-dose weekly paclitaxel, which I suppose you could call metronomic, compared to q2 high-dose, or dose-dense, is open, so we do not have an answer.

For other drugs, we would need to make comparisons to provide you with an evidence-based answer. That said, my heart lies with low-dose, less toxic therapy, especially in the palliative setting. I do not disagree with those who advocate metronomic chemotherapy as palliation for incurable disease, although I am a little less convinced that we have meaningful data yet in the adjuvant setting. Clearly, we, and others, are continuing to study this.

FC: I totally agree and I believe that we should probably test both, but my feeling is that what we call metronomic is probably better for the advanced setting, while dose-dense therapy makes more sense for the early setting. We need to let the trials end.

Q: *Do you have any data about the long-term risk of leukaemia by adding G-CSF to dose-dense regimens for breast cancer?*

CH: That was one of the interesting observations that we made – when we give AC across all of our CALGB studies, long-term follow-up averaged out at about a 0.5–0.7% incidence of acute myeloid leukaemia (AML). For our patient population, nearly half of those leukaemias are expected based on the natural history ageing rather than treatment.

We have never demonstrated that growth factor support for a dose-dense regimen was associated with any increase in risk. For example, the incidence of AML in our study was 0.7% with q2 and q3 and was, paradoxically, higher with the sequential regimen in one of the comparisons and the concurrent regimen in the other.

The NSAPB saw a significant increase of AML early on with dose-escalated cyclophosphamide and G-CSF support. When they gave 2400 mg/m^2 of cyclophosphamide q3 with growth factor support, they saw an increased incidence, and I recall going to the National Cancer Institute in the 1990s to talk about whether this was worrisome. The problem here is that high-dose cyclophosphamide is clearly leukaemogenic. The dilemma is whether it is the growth factor causing this or the high-dose cyclophosphamide. In that context, CALGB 97-41 shows no difference in leukaemia with or without G-CSF. But where the doses are controlled and steady, I think it is probably not the case that G-CSF is contributing anything in terms of AML and lymphoma risk.

FC: If we look at non-dose-dense chemotherapy and the use of G-CSF in these situations, there is no conclusive evidence of an increased risk of leukaemia/lymphoma in patients who need G-CSF, either as primary or secondary prophylaxis.

Q: *What could be the role of dose-dense chemotherapy in the neoadjuvant setting?*

CH: This question is not coming up quite as much these days, but used to come up quite a lot. Looking at the data, people are convinced of the benefit of giving dose-dense therapy postoperatively, but when I am trying to shrink a cancer preoperatively, I would give q3. This is because we do not yet have the right data to prove that a dose-dense regimen is better preoperatively.

Picture this

The new imaging techniques that can help doctors select the right treatment at the right time

Anna Wagstaff

The more we learn about biological variations and changes within a tumour the more daunting becomes the challenge of personalising therapies. New imaging techniques that track the behaviour of key biological markers and processes could offer an elegant way forward. Researchers are calling on the clinical cancer community to join the effort to speed up transition into the clinic.

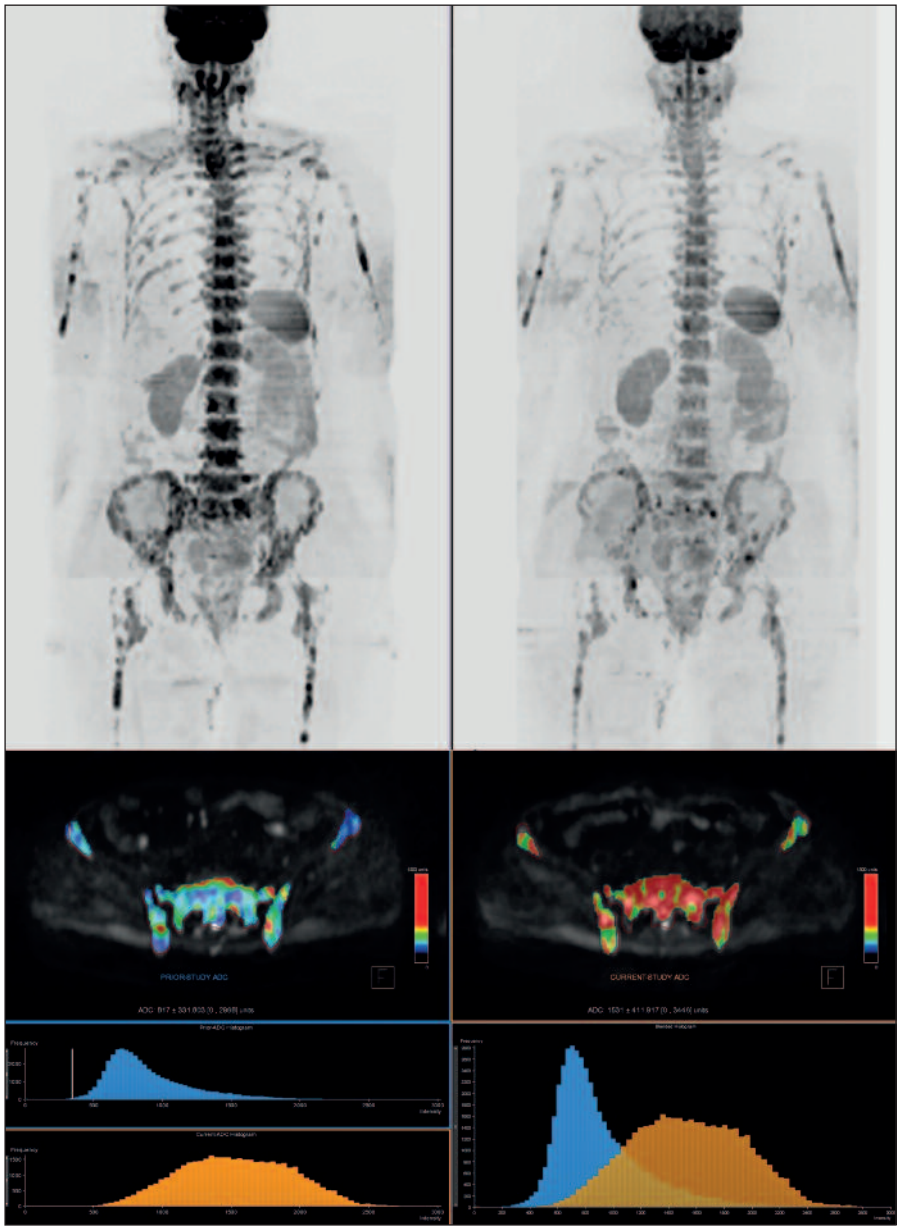
On the road towards personalised cancer therapies, the tasks of identifying new targets and devising ways to hit them seem to be coming along quite nicely. Right now, the big challenge is all about finding ways to work out which of the rapidly expanding selection of therapies will work best for the patient in front of you. Clinicians are crying out for validated cost-effective and patient-friendly methods for gathering biological information ('biomarkers') that help them to select the most appropriate therapy option.

Some of these biomarkers are already well known – the FISH test for HER2 amplification predicts response to therapies designed to block HER2 signalling, such as trastuzumab or lapatinib, while KRAS mutation is a marker predicting resistance to EGFR inhibitors such as cetuximab and panitumumab. And long before these, oncologists were using levels of oestrogen receptor and progesterone receptor as markers for response to hormonal therapy, for instance in breast cancer.

Progress can be seen in the way that pathology labs are introducing an increasing number of tests for biomarkers into the diagnostic routine. Outside the hospital setting, a whole diagnostics industry is mushrooming to provide testing kits to hospital labs and to offer diagnostic services for more high-tech tests. Examples include Genomic Health's Oncotype Dx multi-gene assays and the Agendia and Affymetrix genomic microarrays, which can be used to help select patients for adjuvant chemotherapy – technologies developed initially for use in breast cancer, but now introduced across a variety of cancers.

Progress is also taking place in an area not so well known to the oncology community. The next big thing in biomarkers may be all about 'functional' imaging, which tells you not what a tumour looks like, but about what it is up to biologically. Two imaging technologies in particular are exciting interest for the potential they offer to help inform clinical decision making. The most surprising, perhaps, is MRI. Valued for decades for its ability to provide anatomic images of soft tissue lesions, this technique turns out also to have potential for imaging tumour microenvironments and cell

Whole-body diffusion-weighted MRI



COURTESY OF ANWAR PADHANI © ANWAR PADHANI

Are my patient's bone metastases being controlled by her current therapy? This question, which standard imaging techniques can throw little light on, can be answered using diffusion-weighted MRI scans which map cell density and cell death. The answer in the case of this 65-year-old woman with metastatic breast cancer, would seem to be 'yes', as revealed by comparing the signal intensity of the whole body scans and the ADC (apparent diffusion coefficient) values before (blue histogram) and after (orange histogram) three cycles of treatment with FEC (5-fluorouracil, epirubicin, cyclophosphamide) and bisphosphonates. Higher ADC values are consistent with effect of tumour cell-kill

metabolism – necrosis, cell density, metabolism, tissue perfusion and oxygenation. This can provide vital information about the nature of a tumour and how it is responding, or likely to respond, to a given therapy.

The other technique of interest comes from the field of nuclear medicine, in the form of PET (positron emission tomography) or SPECT (single-photon emission computed tomography). These techniques make it possible to visualise how an injected substance moves around the body by 'labelling' it with a tiny amount of radioactive tracer.

Oncologists will be familiar with the increasing use of FDG-PET for measuring response to treatment, particularly cytostatic treatments of solid tumours, where response typically does not take the form of tumour shrinkage, with the result that traditional anatomical imaging using CT or MRI can be misleading. This PET procedure uses FDG, a glucose analogue labelled with a fluorine radio isotope (^{18}F-fluorodeoxyglucose), to map levels of glucose uptake around the body. This is in the process of being validated as a RECIST (Response Evaluation Criteria In Solid Tumours) marker of early response.

Glucose uptake – a generic marker of tumour activity – is only one of a number of markers of interest for clinical decision makers. The PET technique, in theory at least, can be adapted to map any biological process or molecular marker that can be delineated by a labelled compound that can safely be used in a patient. This includes specific targets such as oestrogen, HER2 or EGF receptors, as well as more generic biological markers of hypoxia, cell proliferation, and cell death.

A new generation of PET-MRI scanners has addressed many of the technical and practical challenges of

functional imaging. The question now needs to be answered for both PET and MRI: in what way can they contribute to the everyday practice of personalised cancer therapies?

An alien in the imaging world

Elisabeth de Vries is a professor of medical oncology at the University Medical Centre Groningen, in the Netherlands. So convinced is she of the potential value of imaging for clinical decision making that she has waded in as "an alien in the imaging world". Her recent research efforts have focused on investigating the clinical use of PET/SPECT, and more recently fluorescence imaging.

de Vries believes these imaging techniques offer a way to address some of the knottiest problems in personalising cancer therapies – not least, the growing recognition that the biology of a tumour can vary markedly from one area to the next and metastatic lesions do not necessarily resemble the primary tumour. "We all want to move to personalised medicine. We want to know who needs what drug either before or early during treatment. But one of the things that I find remarkable is this heterogeneity in tumour lesions. Tumour biopsies provide only static information on the status of a marker in a small part of the tumour and disregard the remaining tumour and possible metastases. Imaging can give us a better whole-body picture and insight into all lesions." What's more, she adds, because it is non-invasive it can be used repeatedly.

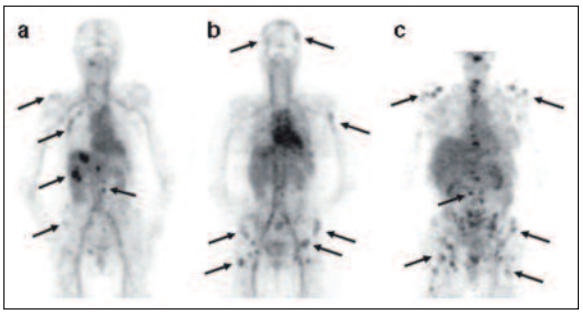
Access to this level of information can be particularly important in cases where standard diagnostic tests are giving conflicting information, says de Vries. "You have a patient with two breast cancers, for instance – one on the right and one on the left. This patient develops metastases, and they are hard to biopsy. You know one primary is oestrogen receptor positive and the other is not. If you can do a PET scan using ^{18}F-oestradiol [FES], which binds to the oestrogen receptor, you can confirm whether or not ER is present on the metastasis" – potentially important information when it comes to choosing a therapy.

de Vries is setting up a prospective study in three Dutch centres enrolling patients with non-rapidly progressive metastatic breast cancer. The study will assess the added value of FES-PET and ^{89}Zr trastuzumab-PET (using tiny quantities of radiolabelled trastuzumab) to predict non-response to targeted treatment with hormone or anti-HER2 therapy before therapy initiation, and of FDG-PET to predict non-response early during drug treatment. "What you want to prove is that it does make sense to get insight into whole-body tumour expression of ER and HER2 to make treatment decisions," she says.

For de Vries, that study represents only one example of many potential uses for molecular imaging. The technique, she argues, is a perfect tool for understanding how to use targeted therapy. As these therapies, by definition, are designed to hunt down a target, if you want to know the extent to which the target is present in a given patient, all you have to do is circulate a trace amount of the product with a radiolabel attached. Potentially these techniques could also be very helpful to evaluate whether targeted drugs are achieving the desired effect on their target in any given patient. In a number of preclinical studies, de Vries and colleagues have demonstrated the impact of a variety of targeted drugs on the expression of the relevant genes as visualised on PET imaging. They are now conducting clinical trials to visualise the effects of drugs specifically on ER, HER2 and VEGF expression.

Molecular imaging can probably even help with identifying the appro-

WHOLE-BODY PET IMAGES USING RADIOLABELLED TRASTUZUMAB



Source: EC Dijkers et al. (2010) *Clin Pharmacol Ther* 87:586-592. Reprinted by permission © Macmillian Publishers Ltd

These PET scans using zirconium-89-labelled trastuzumab map amplified HER2 expression throughout the body in three patients. A prospective clinical trial is being set up in the Netherlands to evaluate the added value of using scans like this to predict non-response to anti-HER2 therapy

"Radiolabelled PET is a perfect tool for understanding how to use targeted therapy"

priate dose, she says. "For instance, we know from clinical trials, and also from our own work, that if you study the pharmacokinetics of trastuzumab in the blood, it varies considerably from patient to patient. This seems to be related to a large extent to the total tumour volume in a patient, which makes sense: if your antibodies specifically go to tumour lesions, there will be a larger sink for the drug – and therefore more drug required – if you have more tumour on board." One implication might be that we may be using more trastuzumab than is necessary in adjuvant settings.

Right now de Vries is actively exploring the potential for using fluorescence as an additional cheaper, easier and safer alternative to radioisotopes. The concept is identical to PET scanning, except that the chosen compound is labelled with a fluorescent marker. de Vries says that the advantages are that you don't need radioactivity, and fluorescence is also better at detecting very small lesions. "You need only a few cells to get the signal. Often for PET scanning you need a lesion to be between 0.5 and 1.0 cm to detect it." The main problem at the moment is that it is impossible to get a whole-body reading, given the limited penetration of light. "Happily several interesting novel devices are in development that are able to detect fluorescence, for instance during surgery, by endoscopy, with a handheld probe or using diffuse optical tomography to identify fluorescence-labelled lesions in the breast.

de Vries is now keen to join multicentre imaging trials in collaboration with US and European centres. She may feel herself to be something of an alien in this field but the traffic is not all one way. Plenty of imaging specialists are now crossing the border in the other direction to join forces with the clinical cancer community to see how techniques they have spent years developing can function in the real world.

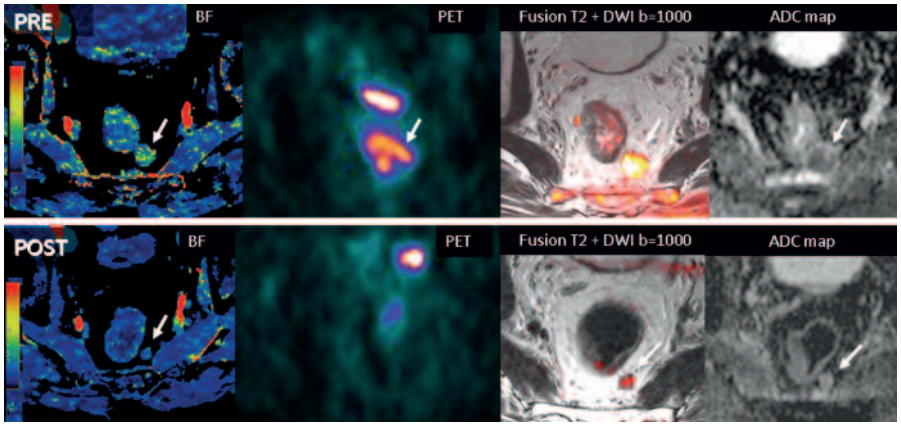
An all-round picture

One of these travellers is the current president of the International Cancer Imaging Society, Anwar Padhani, a radiologist at the Paul Strickland Scanner Centre in London. Padhani shares de Vries' belief that imaging could offer a vital tool for personalising therapies, but his interest is not so much on imaging molecular targets that may be specific to a cancer phenotype, as building up an all-round picture of how a tumour is sustaining itself and how it is responding to treatment. Learning how to do this effectively could be of enormous benefit to speed up drug development and cut costs as well as making it easier to take informed decisions on the management of individual patients.

Angiogenesis, for instance, is known to be important in delivering the oxygen and nutrients that growing tumours need, and radiologists have developed a technique – dynamic contrast-enhanced (DCE) MRI/CT – that can provide whole-body images of the rate of contrast medium uptake, which is a marker for vascularisation. 'Before' and 'after' imaging can tell you how effective anti-angiogenic therapies such as bevacizumab and sunitinib are in a given patient. However, further research is needed to see how accurate imaging is at predicting response and patient benefit.

Exciting though this may be, Padhani is looking for something more comprehensive to guide the use of multitargeted

MULTIMODALITY IMAGING: AN ALTERNATIVE TO THE RECIST CRITERIA OF RESPONSE?

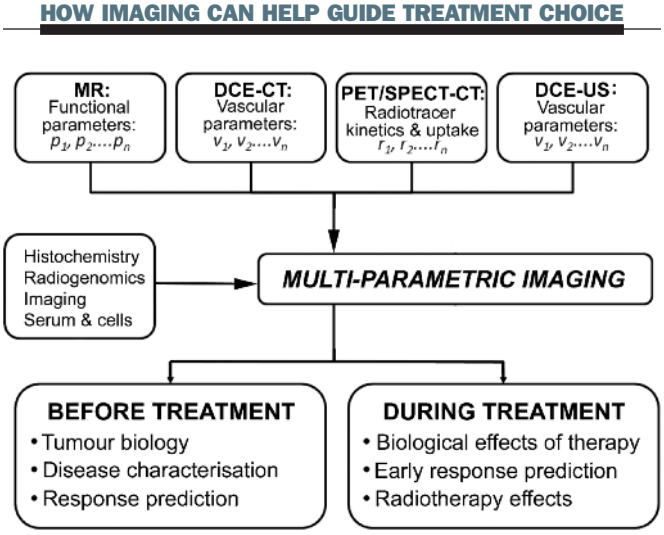


Combining different imaging techniques into a multiparametric evaluation can provide information on multiple biological behaviours of a tumour, which can help guide treatment decisions. This set of images of a T3N1 rectal cancer with mesorectal nodes, taken before and after treatment with chemoradiotherapy, provides information on (*from left to right*) angiogenesis (no increased blood flow (BF) on perfusion CT scan), metabolism (a decrease in glucose uptake and retention on FDG PET) and cell death (an increase in ADC values on diffusion-weighted MRI). Taken together they provide a picture of a good response to treatment, which correlated with the downgrading of the tumour to T1N0 on post-treatment pathological analysis

Source: Courtesy of Roberto Garcia Figueiras, University of Santiago de Compostella © Roberto Garcia Figueiras

"There are many challenges to overcome before they can be introduced into clinical practice"

therapies. "Just because you alter the blood vessels in a particular tissue doesn't mean that patients will benefit. You also need to look at what is happening to other processes in the tumour environment. If you kill some cells but make the tumour hypoxic in the process, you can make things even worse, because we know that hypoxic tumours are more resistant." Getting information on hypoxia requires different types of imaging, such as PET scanning using ^{18}F-misonidazole or ^{64}Cu-diacetl-bis (N4-methylthiosemicarbazone). There are also scans that can help show the extent of cell death (such as diffusion-weighted MRI), or levels of proliferation (PET using ^{18}F-fluorothymidine or ^{11}C-choline) or glucose metabolism (FDG-PET).



Using multiple imaging technologies before and during treatment can help characterise the tumour tissue and assess how it is responding to therapy

DCE-CT – dynamic contrast-enhanced CT; SPECT – single-photon-emission CT; DCE-US – dynamic contrast-enhanced (microbubble) ultrasound.

Source: AR Padhani and KA Miles (2010) *Radiology* 258:348-364. Reprinted courtesy of Anwar Padhani and the Radiology Society of North America

As many of these processes are linked, it is not always straightforward to interpret the signals. Tumour cells that are starved of oxygen, for instance, tend to respond by switching on more glucose receptors. The FDG-PET scan will tell you where glucose metabolism is upregulated, "but is that because it is more hypoxic or because the tumour phenotype is intrinsically producing more receptors?" Either way, he adds, you know you have an aggressive tumour.

This array of imaging tools offers potential for understanding what a patient needs and how they are responding to selected treatments. But Padhani says there are many challenges to overcome before they can be introduced into clinical practice. These include the issue of how many tests you can do multiple times (cost, logistics and toxicity can be factors here). Then there is the issue of how imaging information is complementary to other biomarkers such as circulating tumour cells, tumour markers, urine biomarkers, immunohistochemistry. "Where does imaging fit in, how does it correlate with these other biomarkers? There are exploratory investigations into this area but they have not progressed far," says Padhani. He reviewed some of these issues in a paper he co-authored on Multiparametric Imaging of Tumour Response to Therapy, published in *Radiology* in 2010 (vol 258, pp 348–364).

There is also a question about proof of clinical benefit. "A lot of this imaging hasn't yet been correlated with patient outcomes. For FDG-PET we have firm evidence that changes in PET scans actually affect how patients feel and how they survive. This has been shown and in a number of different cancer types, including as a marker of response. But for the vast majority of others it hasn't been done, and the roadmap of how to do it has not been defined."

He and his fellow researchers are calling on oncologists to get engaged in this work. "We can't do it ourselves. We can develop the techniques, but we need active cooperation from the oncologists to be able to take the technique forward, to find its role, what its 'killer app' is going to be. The landscape will change and they will need to become much more familiar with imaging as we need to be familiar with what they do. We need to do this together."

Speeding progress to the clinic

Efforts to progress the use of imaging in personalised therapies have been concentrated in countries where major research bodies are capable of taking

on this task, such as Germany and the UK. Harpal Kumar, chief executive of Cancer Research UK, for instance, recognised in 2008 that "imaging is fast becoming one of the most effective means of detecting cancer early and of determining which treatment works for which patient." The charity almost quadrupled its funding for this area of work to £50 million (€58 million euros) over five years. A lot of work is also being done in the US, which applies a lighter regulatory hand to the use of new radioactive tracers for investigational procedures.

EU funding for developing imaging biomarkers was boosted in 2006 with the Innovative Medicines Initiative (IMI), a €2 billion EU–industry partnership. Some of this is targeted to:

- create disease-specific European Imaging Networks,
- develop regional centres of excellence, creating disease-specific European centres for the validation of new biomarkers and
- enhance collaboration with patients and regulatory authorities.

The EORTC has already secured funding for a trial investigating the value of diffusion-weighted MRI and PET imaging for proliferation and apoptosis for use as surrogate markers in early clinical trials.

Leading this work is Sigrid Stroobants, head of the Department of Nuclear Imaging at the University of Antwerp, and chair of the EORTC's Imaging Group, which was established in early 2010. Stroobant's imaging group scans all new trial proposals submitted to the EORTC to identify opportunities for tacking on an imaging study to the protocol. She says that a lot of observational trials with imaging are needed simply to relate the signals they find to what they see in preclinical studies without interfering in the treatment.

Such imaging add-ons can be very expensive, however – around €500 for an MRI scan, €800 for FDG-PET, and closer to €1000–1500 for other PET tracers, which are not so widely available. There is also a question of capacity. The EORTC imaging group is coordinating with the UK imaging network set up by Cancer Research UK, and between them they cover around 100 centres, but not all of them can do what is required. "Not all clinical centres have the capacity to do these high fancy imaging techniques and you sometimes see a discordance between what we need for imaging and what we need for the clinical department. Sometimes they lack the special sequences we need for diffusion MR or they don't have access to FLT [^{18}F-fluorothymidine, an alternative PET tracer]."

Stroobants believes that some of the more generic markers that Padhani talks about are good candidates for replacing the traditional RECIST criteria for measuring response in many situations, using FLT- and FDG-PET scanning and probably dynamic contrast-enhanced MRI and diffusion-weighted MRI. She believes that the diffusion-weighted MRI technique may develop to the point where it may start to be used in preference to FDG-PET scans, which are more expensive, involve radioactivity, and are logistically more demanding.

But there is a lot of work to do before this technique can be used in multicentre trials because there is no standardisation yet, and still a lot to learn. "Very simple things that can influence the signals are not known yet. Does the patient need to be fastened in a fixed position or not? What influence does the use of contrast enhancement have? Does it depend on the age of the patient?"

Cross-calibration is required before MRI can be used in multicentre trials, to make sure that differences between images from different centres represent real biological differences and not just different machine settings, and this is one of the work packages from the IMI project. "We hope with the extra funding we received from the EU we will be able to solve that problem, let's say within one year's time," says Stroobants. I'm hoping that within five years we can validate these as biomarkers of response."

Key to carrying out such multicentre studies will be the imaging platform that EORTC has developed in coordination with Cancer Research UK, which will be used to collect the images centrally and conduct centralised analysis. An imaging 'warehouse' has also been established which will link to information on clinical data, tissue, blood and plasma samples stored in biobanks.

The challenge is to find the funding to conduct these trials and to convince clinicians that it is worthwhile taking them on. Stroobants says this can be very hard to do, but that larger multicentre trials are needed. "It is important that we try to incorporate imaging in trials and that we move away from doing single-centre studies and trying to analyse data in our own way. This will not move the field forward. We need to think bigger, multicentre, standardised – the time to play in individual centres is over."

"We need to think bigger, multicentre, standardised – the time to play in individual centres is over"

Is hope worth any price?

Award for German reporter who tackled a subject many prefer to avoid

When every additional day of life matters on the one hand, and the interests of a multibillion dollar industry are at stake on the other, promoting an informed debate about reimbursement policies can be quite a challenge. Freelance journalist **Martina Keller** won a Best Cancer Reporter Award for her contribution, which was published in the German daily *Die Zeit*, under the title 'The price of life' and is reprinted here.

Hope – its colour is white for Wolfgang Behling and it has come into his life through a pill. Afinitor is the name of the drug he has been taking, 10 mg per day, for five months – a period of time he is grateful for, because he does not take a week, or a day, for granted since receiving this diagnosis: kidney cancer at an advanced stage.

Behling hardly looks ill. He is slim but not skinny, with thick grey hair. In the living room of his detached house an open fire is blazing, and Behling is looking through a large window towards his garden. He had a birthday party here last August when he turned 50, with a big fireworks display. A neighbour called the police about the noise, but Behling didn't care. To make it through another year is a reason to celebrate. "The question is not whether I shall die from this illness but when," he says. "And I hope that my new drug will stop the cancer cells from spreading for as long as possible."

Median survival for patients like Wolfgang Behling is about 15 months. Behling is now in his fifth year. Recently he celebrated his 28th wedding anniversary with his wife. He was there when his daughter turned 17. And he booked a short family break during her school holidays at the end of January. His planning horizon is not as far ahead as for other men of his age who believe themselves to be in their midlife – but nevertheless Behling has the courage to plan his near future again.

Martina Keller

All that is partly thanks to Afinitor, Behling believes. "I fell ill in good times," he says.

Until just a few years ago Germany's doctors were not able to offer much to patients like Behling. But since 2006, six new, very expensive drugs have been approved for the market – Afinitor from Novartis is one of them. Thanks to these drugs there has been a genuine revolution, some cancer specialists enthuse – grateful finally to be able to prescribe

DOSSIER

WOCHENSCHAU

GESCHICHTE

20. Januar 2011 DIE ZEIT N° 4 13

Der Preis des Lebens

3967 Euro im Monat kostet das Medikament, das der krebskranke Wolfgang Behling bekommt. Ob es sein Leben verlängert oder sein Leiden, kann niemand sagen. Sicher sind nur die Profite des Pharmakonzerns Novartis. Ein Fallbeispiel

VON MARTINA KELLER

Moral und Kosten

Kann man so viel für einen Patienten ausgeben? Ja, sagen einige Ärzte – weil sie dafür an der Hilfe für andere Kranke sparen müssen

DIE ZEIT

Getting the balance right. Articles like this one, which dare pose questions politicians and doctors shy away from, are essential for societies to make informed choices about how to prioritise limited health budgets

something to their desperate patients. But other oncologists (specialists in cancer) say: that the pharmaceutical industry profits far more than patients from these drugs, because only their costs are certain, not their benefits.

So – unwittingly – cancer patient Wolfgang Behling finds himself in the middle of a fundamental controversy about drugs – this vast trade in knowledge, speculation and promises of a cure. The debate is about questions that few doctors dare ask: how much is it worth to give patients hope that they may live a few additional days, weeks or months? Must healthcare providers pay any price for every small, even questionable, additional benefit? And where else in the healthcare system should money be saved instead: prevention, hip surgery, dentists' visits to kindergartens?

The history of the drug Afinitor presents an example of this moral dilemma – and an example too of a lack of transparency. In the German healthcare system the moral beliefs of doctors run up against business interests and marketing promises, particularly in such a frightening illness as cancer, which is of major public interest in an aging society and which is viewed by the pharmaceutical industry as a very lucrative market.

Can one spend too much on a patient? Yes say some, if you have to cut spending on other patients to pay for it

In the long and winding road of cancer treatment, patients have repeatedly pinned their hopes on new drugs

The companies ask a high price for every new drug. For Afinitor, Wolfgang Behling's healthcare provider pays €3967 per month. Annually it adds up to more than €47,000. There are even more expensive cancer drugs. Hardly a company is missing out on the new agents: more than 500 drugs are being tested, and around 40 of them will be approved over the coming five years. That could push the German healthcare system to its limits. Already the so-called 'special drugs', among them the anti-cancer drugs, consume more than a quarter of the healthcare providers' drugs budget, even though they represent only two per cent of the prescriptions.

For Afinitor, the Swiss company Novartis has set up a dedicated website. A short animated film demonstrates the medical progress represented by the drug. A feeble local train pulls up at a station, the passengers cross the platform to get on the yellow-gold Afinitor train – and it takes them to a country without limits.

"Highly distasteful", comments oncologist Wolf-Dieter Ludwig. Fifty-eight-year-old Ludwig is chief physician at the Berlin-Buch Helios Clinic and president of the German Medical Association's Drug Commission. "We know perfectly well that patients do not change to a high-speed train, but at best to a regional train," he says. The benefits of Afinitor and of many other anti-cancer drugs have simply not been sufficiently proven, adds Ludwig, who calls the prices "obscene". "That's why we lack money for other treatment options for cancer patients, for example psychosocial support and palliative care."

As for the prices of the drugs, Germany is a paradise for manufacturers. For a start, they are able to fix them as they wish, the prices being barely related to what they spend on research and production. As is common in the pharma industry, Novartis refuses to reveal the costings for Afinitor. When asked to justify the price of several thousand euros per month, David Epstein, a senior executive, says, "In kidney cancer it was fairly straightforward, because there were already other kidney cancer drugs on the market." Those ended up setting a benchmark for what governments would be willing to pay – and those benchmarks were of course calculated by the other companies, "based upon benefits for the healthcare system." In other words: companies take what they can get.

Growing criticism

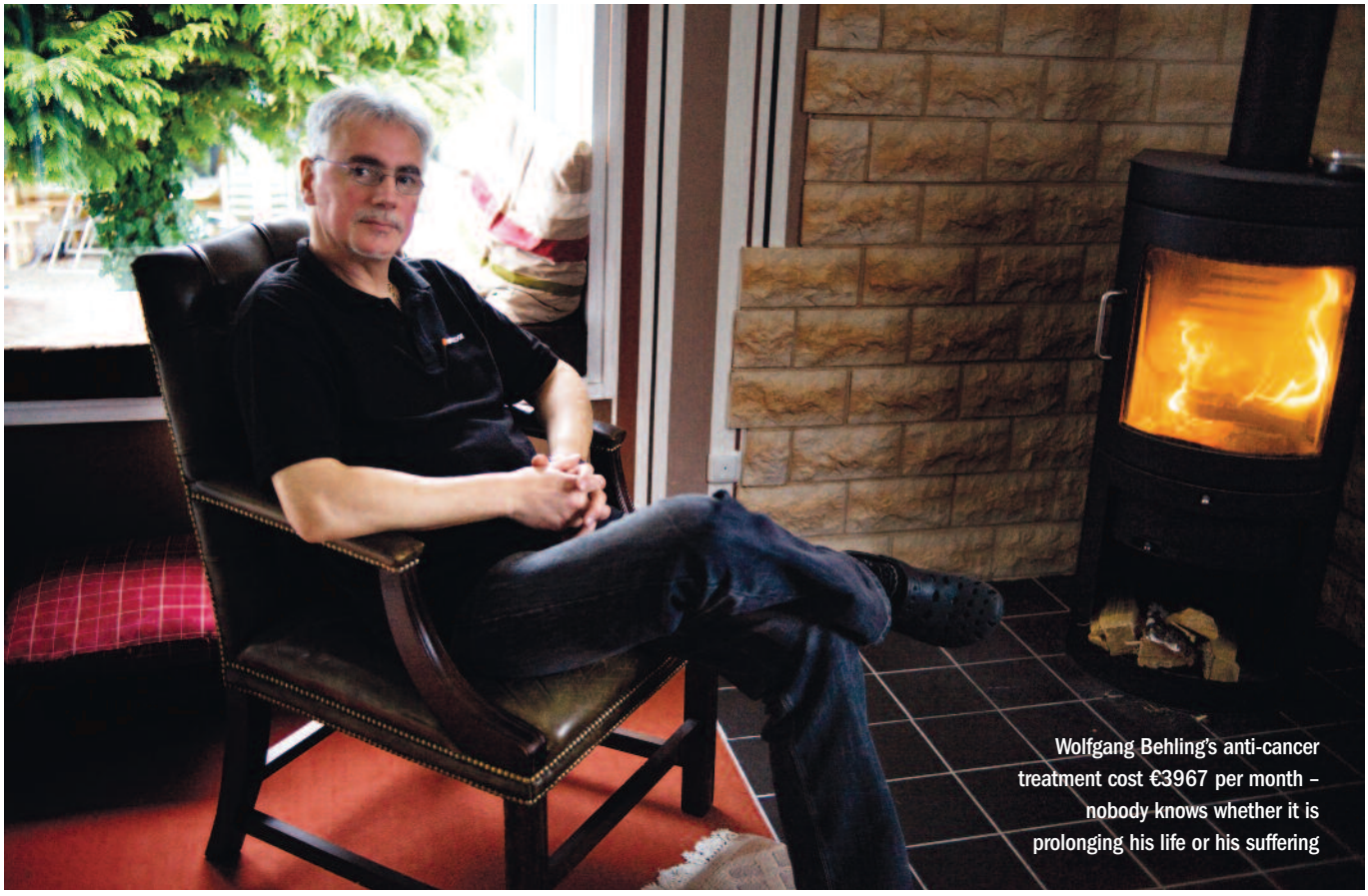
Oncologist Ludwig from Berlin is not the only doctor criticising this industry. He is part of a small but growing group of experienced cancer doctors who are able to speak out more freely than others, because they are independent from the pharmaceutical industry – for example, they don't take fees from pharma companies or they make public any collaborations and studies. Those who share Ludwig's opinions include Arnold Ganser, director of the department of haematology and oncology at Hannover Medical School, Sebastian Fetscher, chief physician at the Sana Hospital in Lübeck and head of the oncology working group of the German Medical Association's Drug Commission, and Axel Heyll, head of the Oncology Competence Centre of the Medical Services [an advisory service to statutory health insurers] in Düsseldorf.

The group around Ludwig has made a fundamental observation: in many kinds of cancer there has been no change in outcomes for decades – contrary to what the pharmaceutical companies' advertisements are suggesting. In the long and winding road of cancer treatment, patients have repeatedly pinned their hopes on new drugs. Many physicians are also grateful for any option – helplessness or even capitulation doesn't fit with their professional self-image.

Under this pressure, medicines agencies grant marketing approvals to manufacturers easily, as soon as there are signs of a better efficacy – who would deny a promising new agent to terminally ill patients on the basis that it would be better to wait for the results of a lengthy clinical study? Scientists like Ludwig, however, doubt whether approvals made under those circumstances are meaningful in terms of the benefits of an anti-cancer drug. They lack proof that a new drug will be even marginally better than a well-proven and cheaper standard drug.

But are mere indications of greater efficacy not enough, if it is a matter of life or death? Should medical science not be obliged to respond to the demand for hope, even when it is only the costs that are certain?

"That's a legitimate question," says cancer patient Wolfgang Behling, "but healthy people's answers will certainly differ from patients'. As a patient, I say: you cannot put a price on life." He would like to celebrate his daughter's 18th birthday; to live to see her school



Wolfgang Behling's anti-cancer treatment cost €3967 per month – nobody knows whether it is prolonging his life or his suffering

ANTONIA ZENNARO

graduation. There are so many things.

Behling has known about his illness since the end of 2006. His general practitioner discovered the tumour during a routine ultrasound. Behling is still astonished that he had not noticed anything till then. "The tumour weighed 1.7 kilos – that's nearly two cartons of milk."

This is the malicious thing about kidney cancer: it takes a long time to start hurting, and therefore often remains undiagnosed until metastases– secondary tumours – have grown. In the beginning Behling hoped to be cured. During his first surgery, in January 2007, the surgeons removed the whole tumour together with his left kidney. But after a check-up six months later, Behling's world fell apart: a new tumour had grown where his kidney had been, and the doctor discovered two metastases in his lung.

Again Behling underwent surgery, and the second tumour was removed. But Behling recovered slowly, and had to be fed artificially for weeks. And the metastases in his lung remained. Now there was no further doubt: short of a miracle, Behling would not be cured.

A year ago the first of the six new drugs against advanced kidney cancer was approved: Sutent. It was prescribed to Behling – and his metastases shrank. "They probably did not disappear, but in the x-ray they were no longer visible," he says. No cure, but he gained time, and Behling was therefore prepared to accept the side-effects: diarrhoea, loss of taste, inflammation of the feet and

Should medical science be obliged to respond to the demand for hope even when only the costs are certain?

hands. Sometimes he was not even able to open a Coke.

Behling came to terms with the illness – and the side-effects. He took his drug in the evenings to avoid being tortured by diarrhoea during the day. He started work again, as head of a tyre retailer. He even wanted to fulfil an old dream: a trip to Canada.

Then the 9th of April came, the tenth check-up. Suddenly the metastases were back. His drug was no longer effective. "I knew, this day would come, but when it did, I nevertheless felt low," says Behling. But still he is not discouraged. Because now there is a new weapon: Afinitor. The next hope, the next promise. Would this drug grant a further delay to Behling, some additional months or years of life?

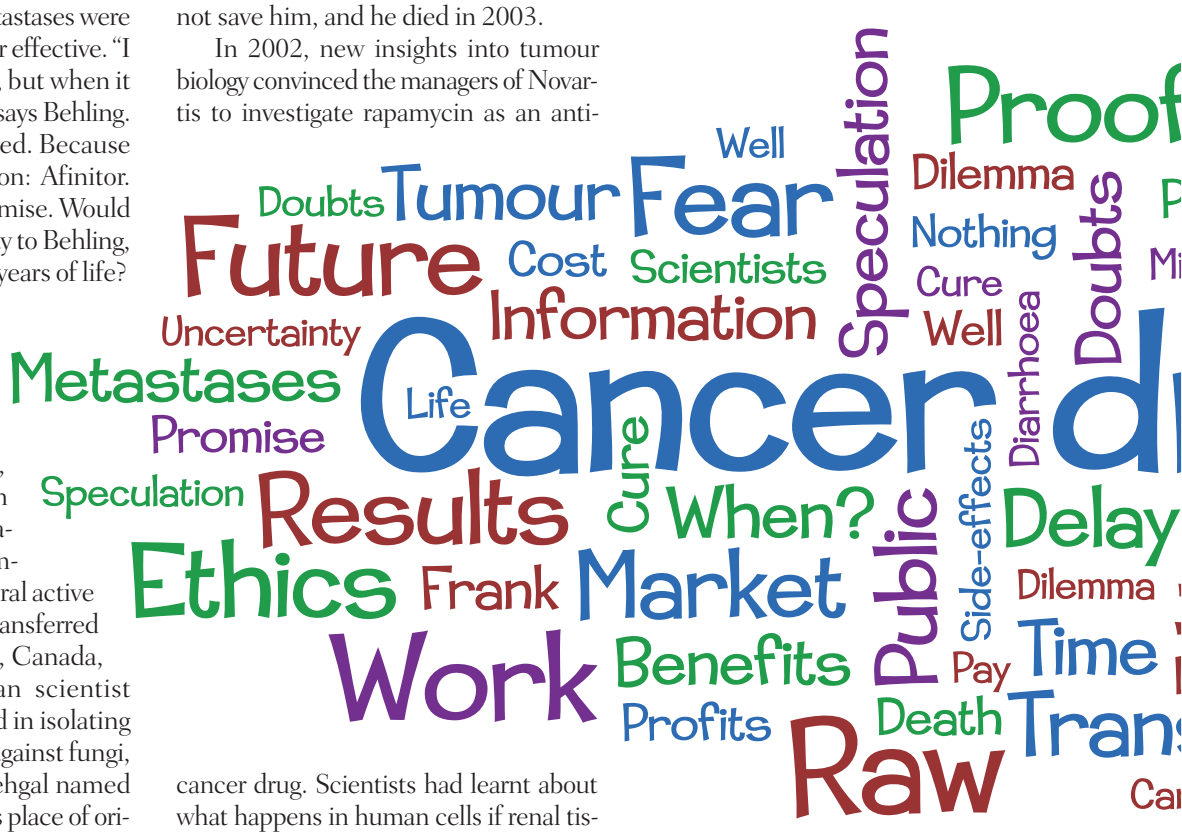
The back story

This still young drug has a long history that is the stuff of legends. It starts in Rapa Nui, or Easter Island, in the south east Pacific. In the sixties a team of Canadian scientists took soil samples there – looking for natural active agents. The samples were transferred to a laboratory in Montreal, Canada, where in 1972 the Indian scientist Surendra Sehgal succeeded in isolating a new substance, effective against fungi, from a bacterial culture. Sehgal named it rapamycin – because of its place of origin. Soon he found out that this rapamycin was also able to suppress the body's immune system, making it of interest for transplantation therapy, which needs this type of agent to prevent organ rejection. Curious to find out whether rapamycin could do more, Sehgal sent a sample to the USA – to the National Cancer Institute. The reply: rapamycin showed "fantastic activity" against cancer cells.

This is the point where the story nearly came to an end, and Afinitor would never have been developed, because in the early eighties the laboratory in Montreal closed. But scientist Sehgal managed to save a batch of rapamycin for his new workstation in Princeton. Some years later, Sehgal fell ill with colon cancer. He is said to have tested rapamycin – which by then had been approved as a drug for transplantation therapy – on his own body against his metastases. It did not save him, and he died in 2003.

In 2002, new insights into tumour biology convinced the managers of Novartis to investigate rapamycin as an anti-cancer drug. Scientists had learnt about what happens in human cells if renal tissue starts growing out of control: specifically, they had found that a certain protein regulating growth and augmentation of cells is overexpressed in these circumstances, and rapamycin is active against just this protein.

In December 2006, the month Wolfgang Behling saw the tumour for the first time on ultrasound, Novartis started the pivotal trial for marketing approval of Afinitor – as it called the rapamycin derivative it had developed. More than 400 patients with advanced kidney cancer took part in the trial, all of whom had progressed on a previous drug. Two thirds of those patients got the new drug, one third a placebo. David Lebwohl, head of Novartis' Afinitor programme, says he well remembers the day when the data monitoring committee told him about "an important effect" shown in the patients. "That was fantastic," he says.



Afinitor had delayed the progression of the kidney cancer for just three months, according to the trial results. Nevertheless, since that time the drug has been looked upon as a potential new anti-cancer bestseller. Novartis has great plans for Afinitor – an international drug career. Having been approved for advanced kidney cancer, Afinitor will now be trialled in other types of cancer, for example liver, breast and stomach cancer. The Swiss market analyst Helvea says that annual

sales could build to a peak of four to six billion dollars for Afinitor alone. In a report published in 2009, Helvea considers the drug as the "single most important asset in Novartis' drugs pipeline." Afinitor could be a future "blockbuster". It seems that the language of the pharmaceutical industry is Hollywood-speak.

But what does this mean for kidney cancer patients? Do they live longer when their illness is kept at bay for three additional months under treatment with Afinitor? The answer is not as obvious as many lay people, or

even physicians, believe. It sounds like a contradiction to say that, if the growth of the cancer is postponed for three months, that does not mean the patients necessarily live longer. But only in advanced colon cancer – and for another drug – has it been proven that a temporary halt to the tumour's growth may prolong life. There are also examples showing the exact opposite: sometimes a drug suppresses cancer cells for a while – but then other, particularly malignant, cells grow all the faster. The temporary stagnation of the illness is followed by an even more rapid progress and the patients probably even die earlier.

To understand more about this issue, the scientific committee of the European Medicines Agency (EMA) had given advice to Novartis on the design of its kidney cancer study, and this advice stressed the importance of demonstrating that patients live longer – or not – when treated with Afinitor.

Novartis ignored the advice of the agency – companies are not forced to comply. When an interim analysis showed that the cancer was progressing more slowly in patients on Afinitor, the company stopped the study. So it missed the chance to find out whether the patients really live longer. As a result, the EMA stated in its evaluation that halting progression of the illness "may not be clinically relevant," because it has not been proven, for example, that the patients live longer.

So why did the EMA recommend Afinitor should be granted marketing authorisation? EMA's press office refers to another quote in the report, which says: based on the data provided, and on reasonable assumptions, a clinical benefit could be considered as "reasonably likely". The EMA is thus accepting some uncertainty – and apparently does not observe its own standards.

Did Novartis discontinue the study because the company did not want to take the risk of losing the good results? What would it mean for the marketing of Afinitor if it had demonstrated only minimal prolongation of life? Or even no prolongation?

David Lebwohl, head of the programme, says his company discontinued the study for ethical reasons: Novartis could no longer deny treatment with Afinitor to patients who had until then been given a placebo.

Cancer specialist Ludwig, the president of the Drug Commission, argues the point the other way round: for ethical reasons Novartis should have continued the study. "If you discontinue a study you take a high risk of overestimating the efficacy of a drug. In addition you will not register side-effects that only become apparent through prolonged observation." As a result, doctors like him lack crucial information: "We don't know which agent is the best, and we don't know which sequence is the best." He, too, uses the new drugs, "but more or less flying blind. And that's the problem."

In this controversy, terminally ill patients like Wolfgang Behling are the test cases. Protest is not to be expected from their side. Even if Behling knows how uncertain is the true impact of Afinitor on his disease, and even though he does not know whether he would be doing better or worse without Afinitor, he believes in its efficacy. "Hope dies hard," he says.

Access versus certainty

The Alliance of Chronic Rare Diseases (Achse), a [German] network of self-help groups for patients and relatives, has fought for years to ensure that new drugs come onto the market as fast as possible – and, like Afinitor, in a fast-track approval that probably leaves important questions unanswered. Achse's reasoning: approval by the European Medicines Agency does prove the additional benefit.

But this is not true in most cases, as Italian researchers found out. They

evaluated data from the EMA. By the end of 2008, 44 drugs had been approved for rare diseases in Europe, but high-quality studies – as prescribed by European drug legislation – were available for just 25 of them.

Real side-effects, uncertain benefits

The patients are the losers. They cannot be sure that their drugs will deliver on the promises the manufacturers make. For an uncertain benefit they have to put up with very severe side-effects. Take, for example, Adolf Kleemann. This 80-year-old has been suffering from kidney cancer for seven years. There have always been long-term survivors of kidney cancer, so nobody knows whether Kleemann's long survival is due to the mild course of his illness – or to all the drugs he has taken. A few months ago, he changed to his fifth therapy.

Kleemann is able to differentiate between the phases of his treatment by their side-effects, which he noted in his therapy log. The first therapy – belonging to an older generation of drugs – he tolerated well. When he changed to the second drug, he suffered side-effects from the very first pill: itchy skin, burning nipples, cardiac pressure, facial swelling, hair loss, swollen hands and severe foot pain. Photos of Kleemann's feet show calluses and raw meat. The skin had come off.

The third and fourth drugs brought other pains to Kleemann: lost of taste, diarrhoea, nosebleed, shortness of breath, bouts of dizziness, constipation, high blood pressure. Sometimes his face was disfigured by heavy inflammation. When he went to his doctor he was always treated first so the other patients in the waiting room did not have to put up with his appearance. Often, he says, he hardly dared leave his flat. "I suffered nearly all side-effects described in the drug information."

Kleemann had to stop taking his fifth drug after two months. He suffered from high blood pressure again, and had to be taken to hospital on suspicion of a stroke. By this time he had tried the last of the recently approved drugs against kidney cancer that his doctor considered to be an option for him. For three months he lived without drugs – and he did astonishingly well. He gained five kilos in weight. But the fear that the cancer in his body might explode does not leave him. He therefore decided to participate in a clinical trial, and now he is on another experimental treatment.

CHRIS GALLAGHER/SCIENCE PHOTO LIBRARY

"I want to live," says Kleemann.

His doctor, Christian Eichelberg, is 34 years old and a senior physician at the University Hospital Hamburg-Eppendorf. When Eichelberg started to treat kidney cancer patients, the first new drugs had just been granted marketing approval. Last summer he again signed a contract in which he agreed to participate in a trial for marketing approval of another drug. This would be the seventh for the treatment of advanced kidney cancer. But how should a physician use all the drugs? When and in which sequence? Eichelberg prescribes by trial and error. He says: "The hardest part for me is to say: I have nothing to offer to you any more."

Wolf-Dieter Ludwig, the chief physician from Berlin, has 25 years more experience than Eichelberg in treating cancer patients. In his opinion, the oncologist has a responsibility not to give false hope to cancer patients in a very advanced stage of the illness. "I would tell the patient: I cannot promise you that this agent will bring you any benefit, perhaps it will bring you just side-effects." Maybe the patient will want to put up with the side-effects to take the small chance that a drug could help him. If so, Ludwig will accompany him down this road. But in his experience, if the doctor speaks frankly, many patients decide against a last aggressive therapy and opt rather for the best available care, so as to live their last days, weeks or months as well as possible.

But many cancer patients in the last stage of their illness do not receive the support they need. While drugs are funded, money is lacking for complex care. "Often patients are tortured by severe pain and find themselves shunted around from one hospital to the other," says Matthias Gockel, senior physician at the Helios Clinic in Berlin. "Here, in most cases, we are able to minimise pain over the course of three days." Gockel is head of the palliative care unit that opened a year ago. Even the furnishing and equipment of the unit is different: the spacious rooms offer enough space to set up an additional bed, in case a relative wants to spend the night alongside the patient. Patients who are well enough may spend their time in a kitchen/living area.

Gockel and his team are specialists at relieving symptoms when a cure is no longer possible. They save their patients from attacks of shortness of breath and suffocation, they treat nausea and dress

stinking wounds so that relatives are able to be close to the patients again. They give priority to the most distressing complaints. For Jürgen Schwedler* it was pain. He is at the palliative care unit because of advanced cancer of the sweat glands. Medical treatment of this 44-year-old man is now so finely tuned that he is able to joke with the art therapist. Schwedler has been fighting for four years: surgery, radiation therapy, medical therapies. Some days he was so weak that he could hardly keep his eyes open while talking. His only wish: "To die in my sleep."

Expert end-of-life care

Whether his wish will come true is down not only to fate but also to the expertise of the treating physicians. Schwedler suffered from a heart attack before he fell ill with cancer. He is therefore getting drugs that should prevent him suffering another attack, which would bring pain and fear of death in his final days. After talking to Gockel, he also decided against resuscitation and intensive care in the event of complications. "What do I gain if my life is extended artificially?" he asks. "It only puts me at risk of dying in pain."

Although waiting for death frightens him, and while he finds it torture to concede he is helpless after his long fight, Schwedler feels well cared for. "When I ring the bell, somebody will come immediately, and when I feel the need to talk, somebody will sit by my bedside holding my hand." The drug costs in the last phase of Schwedler's life are minimal –18 euros per day. But the caring effort is costly: 13 nurses, three physicians, a psychologist, a pastor and several part-time employees care for the 11 patients in the unit.

Many cancer patients die without such support. The German Association for Palliative Medicine estimates that the number of beds in hospitals and hospices is only two thirds of what is needed. In ambulant care the situation is still worse. In some densely populated regions dying patients are well cared for, but in rural areas the situation is often disastrous. Yet the annual costs of treating a single patient with Afinitor could finance half a physician's post. This is another reason the oncologist Ludwig criticises the fancy prices for drugs whose benefits are not proven. For him it is unacceptable that politicians don't force pharmaceutical companies to carry out better studies.

What if the system were to change?

England, for example, has chosen a different approach: because of the lack of robust data, the costs for certain drugs are not covered with no questions asked. First they have to show how the price relates to the additional clinical benefit. Decisions about which drugs the state should reimburse is made by the National Institute for Health and Clinical Excellence (NICE). The basic rule says: an additional year of life in good health has a value of approximately £30,000 pounds, which is €35,000. This is roughly what a healthy person earns per year on average in England.

For the first four of the recently developed drugs against kidney cancer, NICE decided, in a preliminary evaluation in 2008, that the benefits were too low compared to the costs. Following this decision, many patients and relatives demonstrated in front of the London headquarters of the institute, and more than 8000 people signed a petition to the Prime Minister. The *Sunday Times* wrote, "Kidney cancer patients are denied 'wonder drugs'. The protest made an impact: one of the four drugs has since been covered – but with restrictions. In 2010 NICE evaluated Afinitor and decided that the drug was clearly too expensive to merit reimbursement. If the preliminary evaluation is confirmed, the English healthcare system will not reimburse Afinitor.

England, says Novartis manager Epstein, "is not a good place to have cancer. Because England has decided that it is not worth treating cancer patients with drugs."

In Germany the English system is not on the table. Here cancer patients need not be afraid that a drug will not be reimbursed because of its cost. But what if that were to change – what would be the consequence? Cancer patient Wolfgang Behling lost eight kilos since starting on Afinitor. But he has stuck with it – the first drug was even worse, he says.

At the end of last year [2010] Behling again lay down on a CT scanner. On the images the doctor saw a new large metastasis in the lung. He advised Behling to stop taking Afinitor. The drug was no longer effective. Wolfgang Behling now doubts whether it ever helped. "Maybe I lost five months." He is trying another one now.

*Name changed by the editor

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Many cancer patients in the last stage of their illness do not receive the support they need

Still waiting for the world to catch up

The story of Belgium's first ever gynaecological oncologist

➜ Simon Crompton

When **Ignace Vergote** opted to specialise in gynaecological oncology, his country wasn't ready, and he's been waiting for the world to catch up with him ever since. Why has the pharmaceutical industry been so slow to focus on gynaecological cancers? Why must it take so long to get answers to vital treatment questions? And how much longer will his patients have to wait for the sort of quality-controlled specialist clinics Belgium now provides for breast cancer care?

Professor Ignace Vergote is a busy man. Arranging even an hour of his time is a difficult business, and when I meet him in his office at the University Hospitals Leuven, in Belgium, I can't help commenting on his seemingly impenetrable schedule. He looks at me coolly. "But I suspect one of the reasons you want to talk to me is because I'm busy," he says.

He has a point. Vergote, professor at the Katholieke Universiteit Leuven and chairman of the Department of Obstetrics and Gynaecology and the Cancer Institute at University Hospitals, Leuven, is interesting because he has packed so much into his 56 years – as a gynaecological oncologist, researcher, teacher and champion of European collaboration in research and practice. The 'shortened' curriculum vitae he sends me is 79 pages long.

Vergote sees himself more as a European than a Belgian, and he has been a pioneer in developing gynaecological oncology as a speciality in Europe. An investigator on some of the most important clinical studies on gynaecological cancer in the past 20 years, he was a president of the International Gynecologic Cancer Society and of the European Society of Gynaecological Oncology and chairman of the EORTC Gynaecological Cancer Group.

Currently, he is gynaecology section editor of the *European Journal of Cancer*, chairman of the European Network of Gynaecological Oncological Trial groups (ENGOT) and president of the Flemish Society of Obstetrics and Gynaecology.

"You might call me a workaholic," he says. But he suggests this isn't a word he would choose. Instead, the story he tells reveals a single-minded resolution to develop the speciality of gynaecological oncology from scratch in Europe, and then steer it as serenely as possible through the choppy waters of professional territorialism and international differences. Collaboration on an international basis is the only way forward clinically and politically, he believes.

A FIRST FOR BELGIUM

Vergote was the first trained gynaecological oncologist in Belgium. He decided on pursuing the speciality very early in his career. After studying medicine at the University of Ghent, he specialised in obstetrics and gynaecology at the University of Antwerp. His teacher at the time, Frans Uyttenbroeck, was very interested in gynaecological oncology and supported Vergote's desire to train more in the field. The sub-speciality had been recognised in the USA since the 1960s, but on this side of the Atlantic it was well established only in Scandinavia.

So in 1984 Vergote went to the Department of Gynaecological Oncology at Norway's Radiumhospital in Oslo – the national centre for women's cancers. He came back to the University of Antwerp in 1987 to put what he had learnt into practice.

But there was a problem. As a national pioneer in a new speciality, his role in relation to general gynaecologists was not clear, which led to confusion. And he was still required to carry out general obstetrics work much of the time, which was not ideal: "You have to make a commitment to your speciality to get better at it," he says.

So in 1989 he took the radical step of returning to the Radiumhospital in Oslo as a staff member in gynaecological oncology, so that he could "get better". He did. He stayed for another four years, first as head of the Division of Ovarian Cancer and Trophoblastic Diseases, then as deputy chairman of the Department of Gynaecological Oncology, receiving his PhD at the University of Oslo in 1991.

Scandinavia remains special to Vergote – on his office wall hangs a massive reproduction of "Mot Skogen" (Towards the Forest), by the Norwegian painter Edvard Munch, which was painted for Vergote with uncanny accuracy by his goddaughter. He is an honourary member of the Finnish Society of Obstetrics and Gynaecology, and nine years ago he was awarded the Norwegian Kolstad prize for Excellence in Gynaecological Oncology.

Belgium was ready for him on his second return, in 1993. As head of the Division

of Gynaecological Oncology at University Hospitals, Leuven, he was part of the structures of a large referral centre and his role was clear. Gynaecological oncology was now much more firmly established in his home country.

"I think it took this time for patients, gynaecologists and oncologists to realise that there was a need for gynaecological oncologists, especially for cancers in the pelvic area, which can be particularly difficult to treat," he says. "I was not alone any more – there were others who had the same training as me. Together, I think we succeeded in getting acceptance, and the same happened in neighbouring countries like the Netherlands, France, the UK."

On the ward round. Vergote with fellows at University Hospitals, Leuven

A survey carried out by Vergote in the mid-1990s showed that gynaecological oncology was recognised by board certification in only around 35% of countries worldwide. Vergote has been instrumental in encouraging change. As a council member and then president of the European Society of Gynaecological Oncology, he helped set up a system for recognising gynaecological oncology training centres.

"It doesn't have legal status, but recognition from a European society means that trainees at these centres get an official certificate. I think this has played an important role in Europe."

But the battle to gain official board-certification of the sub-speciality – even in his own country – continues. "In Belgium we have waited one and a half years for the government to enact the law that defines all oncological sub-disciplines," he says, "and this applies to digestive oncology and respiratory oncology as much as gynaecological oncology. It still hasn't happened."

Unfortunately, the question of how a gynaecological oncologist's role is defined in relation to other professions is also unresolved in many countries.

A question of how not who

"Who does the chemotherapy is a big question in gynaecological cancers, and it is different from country to country," he says. "It's a big issue in this country, but also many others – in Germany for example, it's the gynaecologist who does the chemotherapy or the medical treatment." His surveys revealed that in the 1990s, medical treatment of gynaecological cancers was given by gynaecological oncologists in around 50% of countries. Breast cancer was treated by gynaecological oncologists in 45%.

"I'd say that both specialities, medical oncology and gynaecological oncology, have their advantages – because medical oncologists have the general internal medicine and oncology training, while we know the disease better and have training that covers surgical and medical treatment."

Vergote is determinedly conciliatory on this issue. He believes in the softly-softly approach to professional problem-solving and chooses every word he says to me with care, almost visibly calculating whether its effect will be positive or negative.

"It's a... challenge," he says. "But I usually say it doesn't actually matter who does it. As long as it's a caregiver who is really committed to concentrating on that disease full time, and is able to work in a multidisciplinary way. In treatment planning ses-

"It doesn't matter who does it, so long as they focus fully on that disease and work in a multidisciplinary way"

"Companies have started to look at ovarian cancer... but cervical cancer is still almost entirely overlooked"

sions here there is always a medical oncologist present, even though gynaecological oncologists give the medical treatment in my department. We discuss the cases together."

But although Vergote is generally a model of tact and moderation, there are three areas where he cannot help revealing frustration. One is the lack of profile that gynaecological cancers have compared to breast, lung and gastrointestinal cancers. He bemoans the lack of cancer leagues and patient support organisations in these areas, in Belgium and other small countries. And while Belgium has breast clinics with set minimum numbers of patients per surgeon and easily accessed nursing and psychological support services, equivalent centres and standards are not available for rare types of cancer like trophoblastic disease, which can be much more difficult to treat. "It's not fair to the patients," he says.

Another area of frustration surrounds the money available for trials of new treatments for gynaecological cancers. When new molecular target therapies were introduced around seven years ago, it was only their applications to the 'big three' markets – breast, lung and gastrointestinal cancers – that had been researched.

"That's why there is still no reimbursed molecular target therapy in gynaecological cancer. It's not because we don't want it, or we're not clever enough. You simply didn't get pharmaceutical companies convinced that they should invest in gynaecological cancer, so the money for trials wasn't there."

At last, he says, now that the market is full of first, second, third and fourth lines of treatment for the big three, companies have started to look at ovarian cancer and are becoming interested in endometrial cancer. But cervical cancer is still almost entirely overlooked.

His own department is now involved in 15 studies on targeted drugs for ovarian and endometrial cancer. Altogether, it produces around 140 papers on obstetrics and gynaecology and 45 on gynaecological oncology every year – and the evidence of its productivity is in the stark corridors outside Vergote's office, where around 100 papers from peer review journals published in 2011 are posted on noticeboards.

The third area of frustration Vergote identifies is the enduring problem of obtaining clinical academic research funding. It is virtually impossible to get support outside the pharmaceutical industry, he says – and this inevitably has a major impact on what is, and what is not, researched.

"Apart from in the UK, there is almost no money available from governments for clinical academic research," he says. "When it comes to pharmaceutical products, this is important because it's clear that when you're working with a pharmaceutical company, you are dependent on them, and there is a danger that you do what is in their interests. We all know that academic trials comparing one treatment with another are almost non-doable, even if it is in the interests of the patients or reimbursement. The same applies to surgery and radiotherapy, which as you know cures more cancer patients than medical treatment."

Promoting academic trials

The urgent need for non-industry trials on drugs and academic trials on surgery and radiotherapy resulted in Vergote founding the European Network of Gynaecological Oncological Trial Groups (ENGOT) five years ago. This is a network of 17 national and regional academic trial groups which aims to make academic trials more feasible through collaboration, and to work with the pharmaceutical industry so that academia has input into industry trials.

But obtaining government funding for their work is not easy. "Recently, as chairman of ENGOT, I wrote to the EU Commissioner for Health, asking if we could get support for some academic trials in endometrial and cervical cancer," Vergote laughs in exasperation. "But we were not listened to. I got a letter back saying that a lot of money had already been put aside for translational research. But that

misses the point, because that money is for laboratory research and not for clinical academic research, certainly not for gynaecological cancers."

The problem is well illustrated by Vergote's own experience. When asked about the research he is most proud of, Vergote points to an academic study published a year ago in the *New England Journal of Medicine*, which was independently funded and has already had a global impact. Sponsored by the EORTC, it analysed outcomes in advanced ovarian cancer surgery according to whether the debulking surgery was timed before or during chemotherapy.

"I was very proud of this. But it took us ten years. We had to randomise 720 patients and, because it wasn't sponsored, people had to be very committed and give their time for free – talking to patients, gaining informed consent, all these things without financial support. It's very difficult. So I am proud of that."

The next big hope

Given the constraints on research, and the time-consuming nature of independent randomised controlled trials, where does the hope for progress in gynaecological cancers lie over the next decade? I suggest that robot-assisted surgery, which Vergote practises, shows real promise for improving surgery outcomes. Yes, he agrees, the potential is there. But nothing is proven – again because of the lack of results from academic randomised controlled trials.

"Even laparoscopy is not proven," he says. "In endometrial cancer, we are still waiting for the survival results of a randomised trial from the US comparing laparoscopy with laparotomy. These types of things take decades."

What about advances in screening? Preliminary results from the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) have indicated that CA125 tumour marker testing combined with transvaginal ultrasound is a feasible mass screening technique. But again Vergote preaches caution. He wrote an editorial in the *Lancet Oncology* pointing out that survival benefit from such screening was not yet proven. He believes that more accurate tumour markers than CA125 need to be found – and his department is working on this problem.

"In 20 years, I think that maybe we will have a marker that will be more specific and good enough for screening. But I think it's still too early to conclude that we have found it."

The real hope for advances that have meaning for patients in the next 10 years come from new drugs and new drug combinations, he believes. They won't necessarily cure more people, but they will lengthen survival.

"When I started in Oslo in 1984, we had only one drug, an alkylating agent, with a median survival of six months. But now, patients progress through an average of four or five lines of chemotherapy, and you also have drugs that obtain a nice response even in platinum-resistant disease. So median survival is now 46 to 48 months. There are now more possibilities of treatment when people relapse, and with the new targeted drugs we will have better drugs to get them in remission with fewer side-effects.

"The new PARP inhibitors for BRCA patients, anti-angiogenesis drugs, alpha-folate blockers and combinations of various targeted drugs – there's so much going on that I believe we will improve survival, but mainly we will delay time to death. Of course, we all hope for the one molecule that will cure cancer or cure ovarian cancer, but it will be a combination of drugs and approaches."

A leading role. Vergote with members of the ESGO Council during his time as president, 2003–2005

In the genes

Vergote's cautious, data-driven optimism probably lies deep in his genes. His father was a finance director working for the Belgian government, and Vergote remembers that both his parents held medicine in very high esteem. No surprise, then, that all four of their children went into medicine or pharmacy. What is more surprising is that all four of those children found spouses who work in medicine, pharmacy and dentistry – Vergote's wife is a dermatologist. Two of Vergote's four children are also entering medicine – one is currently studying, and the other is practising internal medicine – with the other two opting for civil engineering and graphic design. All but the youngest have now left home.

His family has always, he says, been extremely tolerant of his workload. Vergote can think of no hobbies to tell me about, apart from his work. He works every weekend, starting at eight in the morning and finishing at ten or eleven o'clock at night. Yet he says he is a happy family man too. How can this be if he hardly sees his wife and children? "It's not the time that counts, it's the quality," he says – every winter he ensures he gets away for a one-week holiday with his wife and children and their partners, where nothing else intrudes.

So what, I ask, has driven him to work so hard, for so long, focusing not only at a local and national level, but also constantly looking beyond that to the European level?

"I am a European," he says simply. "I am also a Belgian, but I feel our future lies in European co-operation. That's one of the reasons I have supported the EORTC so much, and why I started ENGOT. I believe we work better together. And this isn't just true in oncology but in politics. When I hear about the euro crisis... I find it hard to believe that the UK is not part of the eurozone, for example."

Travelling abroad is also essential for good research, he adds, particularly when you come from a small country. "And it's so important to be able to learn from other countries. In America, they have better communication between their states than we do, but to my mind they are often somewhat narrow-minded. Here in Europe, we are so diverse, and there are so many fantastic things going on. The first breast conservation started in northern Italy and in France – the idea came from Europe before Fisher started his famous studies in the US. But there is still too much nationalism in Europe, and I am keen that this should end."

It's the quality that counts. An all too rare family moment

Our time is up. Vergote's words dry up as he makes it clear there is no possibility of extra time. He has other meetings to attend and patients to see. And it has become clear, over the course of that precious hour, that what drives him on is not so much an addiction to work as an awareness that the tasks that are most worth achieving – whether they be meaningful research or seamless collaboration in Europe – are those that take the most effort… and the longest time.

"Even laparoscopy is not proven... In endometrial cancer, we are still waiting for the results of a US trial"

IMPACTFACTOR

nature REVIEWS CLINICAL ONCOLOGY

The silent minority – unpublished data on cancer care

Daniel F. Hayes

From 1989 to 2003, 709 phase III trials evaluating systemic cancer treatment were presented at ASCO meetings. Tam and collaborators have now reported that 9% of these trials were never published, and 13% were published after a five-year delay. More than half of these studies would have had clinical impact if published promptly.

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Two key elements of the scientific method are methodology transparency and reproducibility of results by others. Traditionally, these elements have been facilitated by the well-entrenched system of peer-review publication. This concept has had almost universal acceptance among the scientific community, although in the past few years there have been calls for open publication of all scientific results without the peer-review process. Some experts have advocated the creation of a type of 'free-for-all' post-publication peer review, with the view that classic, pre-publication peer review is usually selective (based on whom the editor knows and on who actually agrees to referee the article) and arbitrary (based on the respective biases of the reviewers).[1] A search in PubMed with the search terms "journal: Nature" and "all fields: peer review" yielded more than 300 articles, commentaries, and letters extolling the virtues and weaknesses of the system.

Regardless of the outcomes of this debate, at present, the peer-reviewed manuscript remains the gold standard for establishing whether a scientific concept is worthy of further pursuit, and whether there should be a change in the accepted paradigm in the respective field. Although this dictum is accepted in all areas of science, perhaps it is of most relevance in the field of medicine, as acceptance of a new scientific concept leads to a change in clinical practice, thereby affecting the lives of patients afflicted with, or at risk of, a particular disease.

A recent article by Tam et al.[2] in the *Journal of Clinical Oncology* documents a worrisome failure to publish results of phase III randomised trials that were previously reported in abstracts and presentations at the annual meeting of ASCO. They report that, of the 709 abstracts of phase III studies presented at ASCO meetings from 1989 to 2003, nearly a quarter (162 trials including almost 24,000 enrolled patients) were not published in peer-reviewed journals within five years after the meeting in which they were presented. Even after 10 years of follow up, 9% of the presentations remained unpublished. To determine what the relative impact of these studies might have been on clinical practice if they had been published, the researchers queried experts in several of the major cancer types (such as breast,

lung, gastrointestinal and haematologic), who estimated that 38 of 54 (70%) of the unpublished studies "addressed important clinical questions." Although none of the 38 studies was judged to have "critical impact," 32 of them "may have had some impact on clinical practice if the results had been published shortly after presentation."[2]

What can practising physicians learn from these data? Are there any unpublished results that are also unknown to the average physician, and is peer-review publication actually necessary to guide clinical practice? In the days before rapid internet access and widespread attendance at major medical meetings, clinical practice was mostly driven by four factors: publication of data in peer-reviewed journals; expert opinion expressed in published reviews and/or continuing medical education (CME) meetings; pharmaceutical representatives providing drug information; and personal or colleagues' experience. Today, any report presented at a major meeting, without having been published in a peer-reviewed publication, can have a substantial impact on practice. Attendance at meetings has risen dramatically. Nearly 30,000 people attended the ASCO annual meeting in 2010, compared with 3000 in 1980. Furthermore, results from ASCO and other major meetings are now made widely available, occasionally in real time, as webcasts or other media presentations for those not able to attend in person. The effects of these changes on practice are exemplified by the rapid acceptance of adjuvant trastuzumab for patients with HER2-positive breast cancer following the reporting of dramatic reductions in recurrence from four prospective randomised clinical trials at the May 2005 ASCO meeting.[3,4,5] In a survey of practising oncologists conducted in February 2005, fewer than 10% reported that they would recommend adjuvant trastuzumab for a patient with node-positive, HER2-positive breast cancer.[6] In August of that same year, just three months after the ASCO presentation, more than 95% of oncologists said they would recommend adjuvant trastuzumab, preceding the peer-reviewed publications by several months. This sea change in practice was a result of physicians attending the ASCO meeting (36%), attending other meetings in which the ASCO results were provided (56%), and/or hearing about the data in either CME-like publications, audio series or in the lay press.[7]

These considerations, however, do not obviate the need for peer-reviewed publications. Meeting abstracts usually consist of only two to three paragraphs in a proceedings booklet. Often, they do not even include results data, but rather a promise that they will be presented at the meeting. Abstracts cannot replace a complete report that details the design of the study, inclusion and exclusion criteria, dose and schedules used for the treatments and, most importantly, nuances of the benefits and toxic effects of the treatments. This desired level of detail is also not provided by a ten-minute presentation prepared solely by the author (sometimes with substantial influence by a supporting pharmaceutical company) with a five-minute question and answer period. Moreover, the media and public relations coverage at major meetings may amplify the true significance of the results, as they are often fuelled by companies or individuals with vested or biased interests in the drugs involved in the covered studies. So, although it is appropriate to consider an immediate application in practice of paradigm-changing results presented at a meeting, research ethics demand rapid publication of the full details in peer-reviewed publications to guide long-term clinical behaviour.

Furthermore, a single study alone may not change practice. Tam et al.[2] raise a second concern: that the lack of publication may prevent inclusion of important results in meta-analyses of published results, which often confirm or refute conclusions made from a single study. Some meta-analyses have attempted to identify trial reports included in abstracts from major meetings, and others have been able to include patient source data from trials regardless of publication status.[8,9] However, by definition, those meta-analyses that rely on the identification of studies through publicly accessible databases are hindered as a consequence of this lack of publication.

There is a difference in studies that are published compared with those that are not. It has been established that very positive studies are often published very quickly, whereas negative studies often languish on the investigators' desk or are not accepted by major journals and are relegated to journals with lesser impact. This publication bias, as a consequence of either authors' recalcitrance or editors' decisions, is a major concern in regards to making clinical decisions. Tam et al.[2] cite a number of previously recommended solutions for the problem of non-publication of clinical trial data: mandated publication as a condition of external funding or by ethics committee approval; medical journal acceptance of studies with negative results, perhaps in special sections of the journal; and/or

Practice points

- Practicing physicians need to keep up to date with data presented at major meetings as well as peer-reviewed publications
- Investigators need to accept the responsibility for publishing results that they present at meetings

insistence of inclusion of unpublished studies in meta-analyses and expert opinion reviews. They point out that the existence of transparent, publicly accessible trial registries is already in place, enabling interested parties to determine which studies have been opened and/or completed and whether they are published or not. A recently published article has called for such a registry in the field of clinical tumour marker studies, which suffers even more from publication bias than does that of prospective therapeutic trials.[10]

In summary, peer review is not perfect, and could certainly benefit from reform, but to paraphrase Winston Churchill's comment about democracy: "[it] is the worst form of government except all the others that have been tried." It is reassuring that unpublished results represent a small minority of clinical trial results in oncology, but their silence is disturbing. The stakes are high. Patients who participated in these trials did so out of a sense of altruism, and we betray that trust if we do not handle the precious data generated in these studies appropriately. Perhaps more important, future patients' well being and even their lives are at risk, and clinical decisions affecting these patients should not be left to the whims and vagaries of poorly reported evidence. I strongly concur with the reform recommendations and urge those with roles as funders, ethics reviewers, and editors to endorse and enforce them.

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Hodgkin lymphoma – absence of evidence not evidence of absence!

➜ Peter Borchmann, Andreas Engert and Volker Diehl

The optimal treatment for patients with advanced-stage Hodgkin lymphoma is an ongoing controversy. A recent trial seemed to answer some of the important open questions in the field; however, closer examination of the data indicates that the answers are not as clear as they might initially seem.

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The majority of patients (85–95%) with advanced-stage Hodgkin lymphoma can be cured; however, it is currently unclear which treatment strategy offers the best balance between toxicity and efficacy. This key question has been discussed extensively since the introduction of the dose-intense therapy BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone) a decade ago. The efficacy and toxicity of BEACOPP in patients with advanced-stage Hodgkin lymphoma was initially evaluated in the GHSG-HD9 trial that compared it with COPP–ABVD (an alternating regimen of cyclophosphamide, vincristine, procarbazine and prednisone [COPP], and doxorubicin, bleomycin, vincristine and dacarbazine [ABVD]).[1] With 10 years of follow up, the escalated regimen of BEACOPP was clearly superior to COPP–ABVD in terms of tumour control – the difference in freedom from treatment failure was 18% and the difference in overall survival was 11%.[2] However, despite the efficacy superiority of BEACOPP over COPP–ABVD, ABVD alone followed by consolidation radiotherapy

for residual disease (required by approximately 65% of patients) is still commonly being used to treat patients with advanced-stage Hodgkin lymphoma. This lack of change in the treatment paradigm has arisen because COPP–ABVD was not regarded as standard of care by some opinion leaders owing to its similar efficacy but increased toxicity compared with ABVD alone.[3,4]

With regard to the lower efficacy of ABVD as compared with BEACOPP (five-year progression-free survival difference 14%; overall survival difference 8%),[5] those advocating ABVD as first-line treatment refer to the 'second-shot' hypothesis that includes high-dose chemotherapy as late intensification in patients who have progressive disease or who relapse after first-line ABVD. These patients can be rescued with high-dose chemotherapy – the 'second shot'. This strategy results in an overall survival rate of 80–85% for the whole group, including those patients (estimated 25–35%) who require high-dose chemotherapy rescue.

By contrast, an early intensification approach (the 'Kairos Principle') using the more-effective (but also more-toxic) BEACOPP regimen aims to cure as many patients as possible with a 'first shot'. After treatment with BEACOPP, only 12% of patients need consolidation radiotherapy and only 10–15% of patients will relapse,[6] which results in an overall survival rate of 90–95% at five years (A Engert et al., unpublished data). First-line treatment with BEACOPP has been adopted by most European study groups as standard-of-care for advanced-stage Hodgkin lymphoma.

When one considers particularly the survival difference between treatment with ABVD and BEACOPP one might wonder why one should treat young and otherwise fit patients with Hodgkin lymphoma using ABVD. The reason for the persistent use of ABVD in this patient population is the lack of evidence from randomised trials. Only one trial has directly compared BEACOPP with ABVD, and this trial was too small to obtain significance for survival rates.[5] Therefore, there has been a debate on the question of whether ABVD results in preventable death for one in ten patients or if BEACOPP is an unnecessarily aggressive overtreatment for three quarters of patients.[6]

Against the background of this controversial discussion, a recent publication in the *New England Journal of Medicine* has come as a surprise. Viviani et al.[7] report a direct comparison of a modified BEACOPP regimen with ABVD; both regimens were followed by salvage high-dose chemotherapy for relapsing or progressing patients. The aim of this study was to analyse long-term disease control and treatment-induced morbidity.

Although the comparison of these treatment strategies had been eagerly awaited, unfortunately the trial design is inadequate to answer this 'main' objective. The trial was designed and powered only for the primary endpoint (freedom from first progression), and testing hypotheses for secondary endpoints such as overall survival is specifically excluded by the authors (see statistical analysis plan, page 14, section 14.3 in the online appendix).[7] Nonetheless, *P* values for secondary endpoints are presented throughout the manuscript. The 5% overall survival difference in favour of BEACOPP is interpreted by the authors as 'nonsignificant' ($P=0.39$) and an overall benefit for the less-toxic ABVD treatment is concluded; actually, the lack of significance is a limitation of the study, not a result. In fact, the results of this trial are in sharp contrast to the authors' conclusion because there was a survival difference in favour of BEACOPP in line with the significantly superior freedom from first progression, which was the primary endpoint ($P=0.004$).[7] In addition, the conclusions are in contrast to published data showing an overall survival benefit of 8–11% associated with treatment with BEACOPP.[2,5] Thus, if one considers overall survival to be the most relevant endpoint for young patients with cancer, the data presented by Viviani et al.[7] rather support the early intensification approach provided by first-line treatment with BEACOPP.

When making the assessment of which therapy to use in the first-line setting, one should carefully weigh potential risks and benefits and should have a closer look at the data reported. This closer look at the data is, unfortunately, disappointing; not only the design but also the reporting quality of the Viviani et al.[7] study is surprisingly deficient. The manuscript contains numerous mistakes and discrepancies, both within the publication itself and when compared with a previously reported interim analysis of the same trial, as we have outlined in a letter to the authors that has been accepted for publication in the *New England Journal of Medicine*.[8] Furthermore, regarding the important comparison of the toxic effects associated with the two treatments, Viviani et al.[7] emphasise the problem of late toxicities induced by BEACOPP, but they observed three secondary malignancies in the BEACOPP group, and four in the ABVD group. To underline the good tolerability of ABVD, they cite the results from a clinical trial in which only six cycles of ABVD were applied to each patient;[9] however, eight ABVD cycles were administered in their own study. In fact, little is known about the long-term sequelae (for example, infertility, therapy-induced cardiac dysfunction, bleomycin-induced pulmonary toxicity, and quality of life) associated with eight cycles of ABVD. Unfortunately, the authors have missed the opportunity to add important and missing information to the field.

Even though the publication of the data from the trial seems to have some serious limitations, the reported statistic

that 73% of patients might be cured using ABVD as first-line treatment should be accepted and interpreted. The important question then is how to safely discriminate at diagnosis those patients who will respond to ABVD from those who will progress or relapse after ABVD therapy, which unfortunately is still impossible. As long as we cannot detect these patients, who have a difficult-to-treat and life-threatening disease, patients and physicians should be aware of the overall survival difference in favour of BEACOPP for patients with advanced-stage Hodgkin lymphoma. The conclusion that a 5–11% survival difference is not relevant might sound strange or even cynical to some patients.

Needless to say, we should be carefully looking for evidence to provide the best treatment for our patients. Therefore, we rely on properly designed, conducted and reported clinical studies. Fortunately, medicine is more than just politics. With this in mind, we look forward to the upcoming publication of the EORTC 20012 trial comparing ABVD with a modified regimen of BEACOPP in patients with advanced-stage Hodgkin lymphoma.[10] Even more so, we need to enrol patients into worldwide ongoing clinical trials investigating new strategies such as PET-guided response-adapted treatment to restrict more-aggressive treatment to the subset of patients who really need it.

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NEWSROUND

Selected reports edited by Janet Fricker

Study helps define melanoma tumour margins

→ The Lancet

For cutaneous melanomas thicker than 2 mm resection margins of 2 cm are sufficient and safe, a collaborative study between the Swedish Melanoma Study group and the Danish Melanoma Group has found. The study, say investigators led by Peter Gillgren from the Karolinska Institute (Stockholm, Sweden), represents the largest randomised controlled trial of resection margins for thick melanomas.

Surgery is the key treatment for patients with localised cutaneous melanoma, with the standard procedure being removal of the tumour with a safety margin from the edge of the tumour border. A trade-off exists between a wide excision, with consequent surgical difficulties, and the relapse-risk with a narrow excision, which could compromise disease-free survival or overall survival. Complications of wide excisions, however, include bad cosmetic results, lymphoedema, long hospital inpatient stays, frequent need for skin grafts and complicated skin flap reconstructions.

In the current study, between January 1992 and May 2004, 936 patients with cutaneous melanoma thicker than 2 mm at clinical stage IIA–C were randomised 1:1 to have either a 2-cm (n=465) or a 4-cm (n=471) surgical resection margin. The patients, who were aged 75 years or younger, were recruited from 53 hospitals in Sweden, Denmark, Estonia and Norway.

After a median follow-up of 6.7 years, 181 patients in the 2-cm margin surgery group had died versus 177 in the 4-cm margin surgery group (HR 1.05, 95%CI 0.85–1.29; P=0.64). The five-year overall survival was 65% in the 2-cm group versus 65% in the 4-cm group (P=0.69).

"Our data lend support to the hypothesis that a 2-cm margin is safe but a 1-cm margin might be insufficient for patients with a cutaneous melanoma thicker than 2 mm," write the authors.

The advantage of a 2-cm surgical margin, they add, is that the skin can be closed in most cases without skin grafting or skin flaps. A meta-analysis, they conclude, should now be undertaken of all randomised trials of cutaneous melanoma thicker than 2 mm.

In an accompanying editorial, John Thompson, from the Melanoma Institute Australia (Sydney), and David Ollila, from the University of North Carolina (Chapel Hill, North Carolina), wrote, "These conclusions need to be tempered by the knowledge that the originally planned equivalence trial design had a target accrual of 2000 patients, yet fewer than 1000 were enrolled. Thus, the statistical power required for an equivalence trial was lacking."

The next question to be addressed, they say, is whether a 2-cm margin is preferable to a 1-cm margin or whether a 1-cm margin would be sufficient and safe. Another area of importance, they write, is "proper understanding" of the inherent tumour biology necessary for safe excision margins, adding that assessment of margins using haematoxylin and eosin staining is a relatively crude pathological technique.

■ P Gillgren, K Drzewiecki, M Niin et al. 2 cm versus 4 cm surgical excision margins for primary cutaneous melanoma thicker than 2 mm: a randomised, multicentre trial. *Lancet* 5 November 2011, 378:1635–42

■ J Thompson, D Ollila. Optimum excision margins for melanoma. *ibid* pp 1608–10

Treatments help breast cancer hot flushes

→ Journal of Clinical Oncology

Venlafaxine and clonidine offer effective treatments in the management of hot flushes in patients with breast cancer, a Dutch study has found.

Therapies for breast cancer in pre- and post-menopausal women, such as systemic endocrine therapy and chemotherapy, can result in symptoms of hot flushes that affect compliance and treatment outcomes. Both venlafaxine, a selective serotonin-norepinephrine reuptake inhibitor, and clonidine, a centrally acting alpha-adrenergic agonist, are prescribed to moderate hot flushes. However, trials have not been undertaken comparing them with placebo.

Jan Schellens and colleagues, from the Netherlands Cancer Institute, initiated a randomised double-blind placebo-controlled multicentre trial of venlafaxine and clonidine treatment in women with a history of breast cancer. Between October 2005 and August 2009, 102 patients being treated for breast cancer were enrolled from three Dutch hospitals and randomly assigned (2:2:1) to venlafaxine 75 mg, clonidine 0.1 mg or placebo daily for 12 weeks. The hot flush scores recorded combined both the severity (scored on a scale of 1–4) and frequency (number of five-minute periods experienced over a day) in a single measure.

Results show that during week 12, hot flush scores were significantly lower in the clonidine group versus placebo (P=0.03), while for venlafaxine the difference was borderline not significant (P=0.07).

In contrast, analysing the impact over the entire 12 weeks, the reduction compared with placebo in hot flush scores in the venlafaxine group was 41% (P<0.001), but only 26% (P=0.045) in the clonidine group. The frequencies of treatment-related adverse effects were higher in the venlafaxine group.

"Venlafaxine and clonidine are effective treatments in the management of hot flashes in patients with breast cancer," the authors conclude. "The results of this trial agree with the results of earlier trials in which both venlafaxine and clonidine have been studied. However, to the best of our knowledge, this is the first time that venlafaxine and clonidine were compared with placebo in patients with breast cancer over a period of 12 weeks of treatment."

The authors add that the occurrence of more adverse effects in the venlafaxine group may have been related to the dose of 75 mg daily, somewhat higher than previous studies, which started at 37.5 mg.

In an accompanying editorial, Charles Loprinzi, Debra Barton and Rui Qin, from the Mayo Clinic (Rochester, Minnesota), write that the primary weakness of the study is that the patient numbers were too small to reliably identify suspected differences between the two active study arms. "With the currently reported sample size of 40 patients per arm, the power of detecting a 10% difference (effect size −0.32) is only 29%," they write.

■ A Boekhout, A Vincent and O Dalesio. Management of hot flashes in patients who have breast cancer with venlafaxine and clonidine: a randomised, double-blind, placebo-controlled trial. *JCO* 10 October 2011, 29:3862–68

■ C Loprinzi, D Barton and R Quin. Nonestrogenic management of hot flashes. *ibid*, pp 3842–44

Call for changes to NSCLC treatment paradigm in the elderly

→ The Lancet

Platinum-based doublet chemotherapy was associated with survival benefits compared with vinorelbine or gemcitabine monotherapy in elderly patients with non-small-cell lung cancer (NSCLC), the Intergroupe Francophone de Cancérologie Thoracique (IFCT) 0501 phase III trial has found.

Increases in life expectancy in the general population have led to a notable rise in the incidence of lung cancer in elderly people, leading to a median age of diagnosis of lung cancer in developed countries of between 63 and 70 years. The 2004 ASCO guidelines recommend platinum-based doublet chemotherapy to treat advanced NSCLC in fit, non-elderly adults, but monotherapy for patients older than 70 years. However most *post hoc* subgroup analyses of elderly patients enrolled in clinical trials with no upper age limit have shown similar outcomes in younger and older patients, suggesting that platinum-based doublet chemotherapy increases survival in elderly patients.

In the current study, Elisabeth Quoix and colleagues from the Strasbourg University Hospitals in France, investigated whether patients aged between 70 and 89 years fared better on double therapy. Between April 2006 and December 2009, 451patients with locally advanced or metastatic NSCLC and WHO performance status scores of 0–2 were enrolled from 61 centres and randomised in a 1:1 ratio to receive either four cycles of carboplatin plus paclitaxel (n=225) or five cycles of vinorelbine or gemcitabine monotherapy (n=226). In the monotherapy group 62 patients received vinorelbine and 164 gemcitabine. The median age of patients in the trial was 77 years.

Results showed that median overall survival was 10.3 months for the doublet chemotherapy group versus 6.2 months for the monotherapy group (HR 0.64, 95%CI 0.52–0.78; P<0.0001). Furthermore, one-year survival was 44.5% for the doublet chemotherapy group versus 25.4% for monotherapy.

Toxic effects, however, were more frequent in the doublet chemotherapy group. For example, 48.4% of patients in the doublet chemotherapy group experienced decreased neutrophil counts versus 12.4% with monotherapy; and 10.3% of patients in the doublet group experienced asthaenia versus 5.8% taking monotherapy.

"We saw a survival benefit with doublet chemotherapy of such magnitude that we believe the treatment paradigm for elderly patients with advanced NSCLC should be reconsidered," write the authors.

In an accompanying editorial Karen Reckamp, from the City of Hope Comprehensive Cancer Center (Duarte, California), writes, "Older patients dominate the lung cancer population, but continue to be under-represented in clinical trials. Additional studies are needed that enrol adequate numbers of older adults, and include a comprehensive geriatric assessment to provide the knowledge required to properly assess the risk–benefit ratio in treatment decisions, so that a personalised approach can be taken."

■ E Quoix, G Zalcman, J Oster. Carboplatin and weekly paclitaxel doublet chemotherapy compared with monotherapy in elderly patients with advanced non-small-cell lung cancer: IFCT-0501 randomised, phase 3 trial. *Lancet* 17 September 2011, 378:1079–88

■ K L Reckamp. Combination chemotherapy for older adults with advanced non-small-cell lung cancer. *ibid*, pp 1055–57

Intraoperative MRI improves glioma resection

➜ Lancet Oncology

Intraoperative MRI guidance in glioma surgery helps surgeons provide the optimum extent of resection, a German study has found.

Intraoperative MRI systems were developed to help visualise tumour remnants that would otherwise remain unresected. Depending on the type of intraoperative MRI system, installation costs $3–8 million, with surgery reported to be more time-consuming than conventional treatment, adding further to costs. But the true value of intraoperative MRI guidance in modern neurosurgery has not been scientifically validated, with only retrospective cohort series studies undertaken showing the positive effects of such guidance according to the extent of remaining tumour tissue.

In the current study, Christian Senft and colleagues, from the Goethe University (Frankfurt, Germany), set out to test whether the additional expense was justified by prospectively assessing whether use of intraoperative MRI guidance resulted in higher rates of radiologically complete tumour resection than did conventional microsurgical tumour resection. The study represents the first randomised controlled trial to be undertaken in the area.

Between October 2007 and July 2010, 58 patients with contrast-enhancing gliomas amenable to radiologically complete resection were assigned in a 1:1 ratio to undergo intraoperative MRI-guided surgery (n=29) or to the conventional microsurgery control group (n=29). The primary endpoint was rate of complete resections established by early postoperative high-field MRI. Surgeons and patients were not masked to the treatment group assignment, but the neuroradiologists who analysed the MRI data were.

Results showed that 96% of patients in the intraoperative MRI group (23 out of 24) had complete tumour resection versus 68% (17 out of 25) in the control group (P=0.023). The postoperative rates of new neurological deficits did not differ between patients in the intraoperative MRI group and the control group (13% vs 8%, P=1.0). No patients for whom use of intraoperative MRI led to wider resection of residual tumour experienced neurological deterioration.

The investigators found intraoperative imaging led to wider resection of contrast-enhancing tissue in a third of patients in the experimental group, and that MRI-guided surgery added around one hour to the procedure over conventional surgery.

"Our study shows that intraoperative MRI is an appropriate method to improve the extent of resection of malignant brain tumours, comparable to the use of 5-aminolaevulinic acid [used for fluorescent imaging of tumour tissue]," write the authors. The enhanced resection, they add, was not achieved at the cost of increased surgical morbidity.

Whether resection control is best implemented by use of an intraoperative MRI device or by visualisation of tissue fluorescence, write the authors, remains to be seen. Future trials of extent of resection and outcome in brain tumour surgery should not be undertaken without use of either intraoperative MRI or 5-aminolaevulinic acid as a control, they conclude.

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PET scan avoids neck dissection

➜ Clinical Oncology

Neck dissection can be avoided in patients with head and neck squamous cell carcinoma (HNSCC), with two positive lymph nodes at presentation (N2), if post-treatment fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET) has been shown to be negative, finds a UK study.

The role of planned neck dissection after chemotherapy and radiotherapy (CRT) in patients with N2 HNSCC remains controversial due to a lack of randomised clinical trial data. Some clinicians advocate neck dissection after CRT for all patients with N2 neck disease regardless of treatment response, while others support its use only in selected cases with residual neck disease. They argue that post-CRT neck dissection benefits only those patients destined to develop nodal recurrence, while in others it represents an unnecessary procedure associated with high rates of postoperative complications.

Evidence is now accumulating supporting use of post-treatment PET in the identification of patients with residual nodal disease after CRT, who would benefit from post-treatment neck dissection. The idea is to spare patients who would not benefit from the procedure. FDG PET is a functional imaging tool that exploits the increased glucose metabolism in malignant tissues, which accumulate higher

concentrations of FDG relative to the surrounding normal tissues.

In the current study, Tom Roques and colleagues, from Norfolk and Norwich University Hospitals NHS Foundation Trust (Norwich, UK), set out to assess neck control in patients with N2 HNSCC in whom neck dissection was omitted for those who showed negative post-treatment FDG PET-CT results

In the study, 34 consecutive patients with N2 HNSCC were treated with radical intent using sequential chemoradiotherapy, 27 of whom received concomitant platinum-based chemotherapy with their radiotherapy.

FDG PET-CT was undertaken three months after completion of the radical radiotherapy, with neck dissection carried out only in those found to have increased FDG uptake in the neck post-treatment. In the study, 33 patients were observed not to show any increase in FDG uptake and therefore avoided neck dissection.

The results showed that in the 33 patients no regional recurrence occurred after a median follow-up of 39.1 months, leading to a negative predictive value (NPV) of post-treatment FDG PET-CT of 100%.

"A negative post-treatment PET-CT seemed to predict the absence of residual tumour in the neck, with an NPV of 100%, allowing us to safely withhold adjuvant neck dissection," write the authors.

If planned neck dissection had been carried out on their entire cohort of patients by virtue of their N2 disease status at presentation, they add, all of them would have undergone a procedure, with its attendant morbidities, without any improvement to their regional disease control.

The current observations, they write, will need to be confirmed in a larger patient cohort involving multiple institutions.

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Anthracycline alternative reduces cardiac toxicity in HER2-positive breast cancer

➜ New England Journal of Medicine

Replacing anthracyclines with docetaxel- and carboplatin-based chemotherapy in patients treated with trastuzumab (Herceptin) for HER2-positive early breast cancer reduces cardiac complications while maintaining survival, the Breast Cancer International Research Group (BCIRG) 006 study has found.

The significant efficacy shown by trastuzumab in treating first-line metastatic HER2-positive breast cancer prompted its evaluation in early-stage disease. Studies have, however, shown increased cardiac dysfunction when trastuzumab is used in combination with anthracycline-based chemotherapy.

In the current study, lead investigator Dennis Slamon, from the University of California Los Angeles, together with investigators from 41 countries, set out to test trastuzumab with and without anthracyclines to determine whether oncologists could provide effective treatments without resulting toxicities.

In the BCIRG 006 study, between April 2001 and March 2004, 3222 women with early-stage HER2-positive breast cancer were randomised to one of three arms. The first arm received doxorubicin and cyclophosphamide followed by docetaxel (the non-trastuzumab group); the second arm received the same regimen plus 52 weeks of trastuzumab (the anthracycline group); and the third arm received docetaxel and carboplatin plus 52 weeks of trastuzumab (the non-anthracycline group). The primary endpoint was disease-free survival, with overall survival and safety as secondary endpoints.

Results show that at five years the estimated disease-free survival rates were 75% for the non-trastuzumab group, 84% among the anthracycline and trastuzumab group and 81% among the non-anthracycline and trastuzumab group.

The overall survival rates were 87% in the non-trastuzumab control group, 92% with the anthracycline and trastuzumab containing regimen (HR 0.63 vs control, $P<0.001$), and 91% for the non-anthracycline and trastuzumab regimen (HR 0.77 vs control, $P=0.04$)

Altogether there were 21 cases of congestive heart failure in the anthracycline and trastuzumab arm versus four cases in the non-anthracycline and trastuzumab arm ($P<0.001$), and seven cases of acute leukaemia in the anthracycline and trastuzumab arm versus one case in the non-anthracycline and trastuzumab arm. There were also significant differences favouring the non-anthracycline group for arthralgias, myalgias, hand-foot syndrome, nail changes, stomatitis, vomiting and sensory and motor neuropathies.

"Our findings show that we can further exploit this new translational knowledge to optimize efficacy while simultaneously minimizing acute and chronic toxic effects in the adjuvant treatment of HER2-positive breast cancer," write the authors.

In an accompanying editorial Daniel Hayes, from the University of Michigan Comprehensive Cancer Center in Ann Arbor, writes, "Taken together, these data do not clearly favour one regimen over the other. Hence, this trial establishes the non anthracycline regimen as 'another' (but not 'the') standard of care for adjuvant treatment of HER2 positive early stage breast cancer."

The risk for secondary leukaemia or irreversible congestive heart failure from anthracyclines, he adds, is arguably similar to the small but insignificant benefit of the anthracycline regimen over the non-anthracycline regimen (about one to two additional lives saved per 100 patients).

■ D Slamon, W Eiermann, N Robert, et al. Adjuvant trastuzumab in HER2-positive breast cancer. *NEJM* 6 October 2011, 365:1273–83

■ D Hayes. Steady progress against HER2-positive breast cancer. *ibid*, pp 1336–38

After the treatment's over...

Measuring the rehabilitation needs of Europe's growing army of survivors

Peter McIntyre

As more cancer patients survive longer, the need for rehabilitation services is rising up the political agenda, driven by patients who want their lives back, and by policy makers who want people to get back to work, or at least become as independent as possible. To improve services we need to measure rehabilitation needs and service capacity – but that's easier said than done.

The odds that at least one person in a group like this is living with cancer are high and increasing. Many will need help to get back on their feet after their treatment ends

By 2030 an estimated 75 million people will be living with cancer diagnosed within the previous five years, almost 20 million of them in World Health Organization European region. The number of people in Europe living with a diagnosis of cancer is already rising by about one million people a year, as the number of new cases continues to outstrip the number of people dying with cancer.

This is not only a health challenge. In an era of financial turmoil and under-funded pensions, the prospect of an ever increasing number of people living for a long time with a potentially disabling disease frightens policy makers.

Rehabilitation is a hot topic. On the one hand it is an unexplored, expensive and growing cost; on the other hand, if rehabilitation reduces dependency on acute health services and allows millions of people to return to work and an active life, it could prove highly cost-effective.

As one European expert who has been considering rehabilitation needs put it,

politicians want to know "whether to do rehab or build 50 kilometres of highway."

In 2008 the European Commission launched EUROCHIP 3 to enable meaningful comparison of the needs of cancer patients and the capacity of cancer services between countries and regions, with a view to promoting equality of cancer care across Europe. Under one of the work packages, experts were commissioned to draw up a list of indicators that would enable assessment of rehabilitation needs in the 27 member states.

According to the brief, the indicators had to be based on data that could be collected on a population basis via existing cancer registries, and they had to provide an indication of psychological, clinical, psychiatric, nutritional and social services rehabilitation needs.

This has proved a thankless job. The experts found no agreed definition of who needs or gets rehabilitation, while cancer registries collect little data that can be used to assess need. There is not even agreement on what rehabilitation means.

Different needs

People have different needs according to their cancer, the success or otherwise of treatment, their age and gender. For some, the treatment is completely successful while for others the disease or treatment changes what they can do, and even the way they look. Some need physiotherapy; others need surgical reconstruction or psychosocial counselling.

People also have different aspirations. Some want to return to work. Others want peace and dignity in their remaining time. Young people with cancer may have a need for fertility advice and treatment. Everyone quotes the World Health Organization's definition of rehabilitation, but it hardly helps to define what is needed. "Rehabilitation of people with disabilities is a process aimed at enabling them to reach and maintain their optimal physical, sensory, intellectual, psychological and social functional levels. Rehabilitation provides disabled people with the tools they need to attain independence and self-determination."

Prevalence

Piret Veerus from the National Institute for Health Development in Estonia is leading the expert group and points out that since rehabilitation is a process rather than an endpoint, no single indicator can map patient needs. She told the group, "Prevalence is easily collectable and can be a proxy indicator for the number of patients who need rehabilitation, but maybe prevalence by cancer site or by gender and age group is more important."

Hans Bartsch, medical director of the Tumour Biology Centre at Albert-Ludwigs University, Freiburg, in Germany, heads the working group on supportive care, rehabilitation and social medicine for the German Cancer Society. He doubts that prevalence is much of a guide to rehabilitation needs unless more detail is captured. "The spectrum of rehabilitation needs changes over time. In the first year after treatment there are a lot of physical needs and acute psychosocial aspects. After a time the physical needs decrease and long-term recurrence fears arise.

"Lung cancer patients survive two years at best and they have a lot of rehabilitation needs to keep them as independent as they can be. But only 15% of lung cancer patients receive rehabilitation. Of breast cancer patients, I guess 60% receive rehab."

Gill Hubbard, reader at the Cancer Care Research Centre in Stirling, Scotland, agrees that prevalence on its own is not a good measure of the need for rehabilitation. Her centre is pressing the Scottish Government to collect data on recurrence of disease. "Qualitative data on people living with cancer shows that fear of the disease coming back is so strong. You can tell people there is an 80% survival rate, but what they really want to know is what is the chance of my disease coming back. Patient representatives are keen to keep recurrence as an issue. The cancer data people are not so keen, because it is difficult to collect."

To get around the difficulty of collecting recurrence data, various proposals have been put forward for deriving information on recurrence from prevalence data using statistical modelling. The expert group considered the concept of 'conditioned survival', which shows the statistical chances of a former cancer patient dying in the 12 months after each year of survival. They also recommended 'qualified prevalence' as a proxy indicator, which models how many patients will have complications, relapse or metastases. These and other modelling concepts are being worked on at the Istituto Nazionale dei Tumori in Milan from where Paolo Baili is providing technical support.

Return to work

There was a strong feeling that something beyond prevalence was also needed. Miklós Garami, head of Paediatric Oncology at Semmelweis University, Hungary,

"In the first year there are a lot of physical needs. After a time these decrease and long-term recurrence fears arise"

said, "What people want to know is: will I be able to work or not? Can I have children or not? These things are easy to measure but nobody measures them."

Bartsch agreed. "Return to work is the major issue in Germany. The pension fund is responsible. Politicians always ask: what is the percentage going back to work after rehabilitation?"

But most cancer patients are at or beyond retirement age and work may not be at the top of a cancer patient's own list of priorities. Josette Hoekstra-Weebers, head of supportive care at the Comprehensive Cancer Centre Netherlands, in Groningen, suggests that financial pressure may drive the agenda. "Whose need is it really to return to work? The costs of healthcare are going through the roof and in the Netherlands health insurance companies are giving less and less money for rehabilitation."

Despite such reservations, it is still felt that return to work could be an important indicator. Both France and Belgium are looking at how to link different databases to discover how many cancer patients do go back to work.

However, Elke Van Hoof, director of the Belgian Cancer Centre, suggests that 'return to normal life' would be a better test, less open to political pressure. "No-one was interested in the past because most cancer patients died. Now everyone wants to know who is going to pay for our pensions."

Quality of life

Quality of life has been identified as a priority issue, which could be measured using a questionnaire developed by the EORTC (European Organisation for Research and Treatment of Cancer) that is widely used in research. Because of technical, legal and ethical challenges, in some countries collecting these data would require primary care doctors to act as a go-between with patients, and it was feared that the response rate might be low, making samples unrepresentative. Hoekstra-Weebers pointed out that the Netherlands and other European countries use a psychosocial screening tool developed by the National Comprehensive Cancer Network (an alliance of twenty-one cancer centres in the US), but until this is used more widely, she said, it cannot be adopted as an EU indicator.

How do you quantify rehabilitation needs and capacities? Exercise programmes like this one can be important to regain fitness after cancer treatment, but different survivors need different types of help at different times, from different service providers

An attempt was made to find a measure of existing resources devoted to cancer rehabilitation, but social systems were too diverse to find common threads. Moreover the quantity of resources may be secondary to the quality.

Measuring quality

The Belgian Cancer Plan finances support from nutritionists and social workers and others, but Van Hoof says not enough attention has been paid to quality. "There are 300 psychologists counselling cancer patients in Belgium, but only 10% are trained in cancer issues. So far, we don't have any data on quality of care. Most psychologists are not prepared to deal with the specific issues, fears and problems that are experienced by patients. They had an idealistic notion that they were going to help cancer patients, but they see that some cancer patients die or have problems and some are running away from this. It is very important that staff are well-trained and receive support to cope with their own feelings."

Bartsch strongly agrees. "It is not a question of how many psychologists you have, it is what they are doing. In Germany this is work in progress. We have 90 psychosocial centres but only 20 are in a programme of evaluation to look at what they did. I miss in these indicators the qualitative aspects of rehabilitation. The danger is that the commission will say we will give so many millions to each country for psychologists and social workers, but that will not improve the situation."

Hubbard from Stirling says that collecting data on rehabilitation capacity is very complex. The UK has a pyramid model with specialist rehabilitation at the top and general rehabilitation at the bottom. "Capturing data on that is difficult even in our country. We are saying every health and social care professional needs to have some low-level conversation with the patient to ask about work and assess their needs. The patient might then get referred to the specialist. The capacity you want to measure needs more conceptualising – is it specialist or general rehabilitation?"

Palliative care is another issue that divided the group. Jeanne-Marie Bréchot from the French National Cancer Institute pointed out that the (quite high) proportion of cancer patients who die within a year of diagnosis have a need for palliative care that can be considered as a specialised form of rehabilitation. Magdalena Bielska-Lasota from the National Institute of Public Health in Warsaw

"A major part of the national growth is going to cancer treatment, and rehabilitation is required to get the benefit"

agrees. "This is a discipline of oncology which is developing in its own way, but in Europe not much attention is paid to it and it is not funded sufficiently." In Poland palliative care development is included in the National Cancer Plan and the main objective is to improve quality of life for patients with advanced disease. Priority has been given to the development of high-quality palliative care centres and information about pain relief. There is also special support for patients and families in a system known as 'hospices at home'. "The number of hospices is recognised as an important indicator and I would like it to be included," she said. However, there was also a view that hospices are a distinct speciality that should not be considered as part of oncological rehabilitation.

Some proposals

Despite these difficulties, the group has come up with a short list of proposals.

- Two- and five-year prevalence should be collected by cancer site, age and gender. The list will include qualified prevalence and conditioned survival and if these cannot be calculated then the proportion of patients who have not (yet) been cured will be included.
- Quality of life has been given a high priority but will require pilot studies to test the methodology. Return to work will also be included if links can be made between databases and if the data protection problems can be overcome.
- Palliative care will be discussed with the European Association for Palliative Care.
- One innovative idea is to collect data on specialised care – speech therapy for patients with head and neck cancer, physiotherapy for breast cancer patients, dietician support for colon cancer patients, and psychological support for all cancers.

Alongside the recommendations for data collection will be a mapping report and a scientific paper for the *European Journal of Cancer* or other prestigious journal. A recommendation will be made to the European Commission that rehabilitation be given a higher profile within European research.

In Germany, the rehabilitation system – which originated 50 years ago as a fitness and nutrition programme in former TB centres in the countryside – led the way in providing psychological support for patients, and Bartsch says they need to become better at measuring outcomes.

"As we recognised during these meetings, the differences are tremendous and the infrastructure is still a developing process. Countries like the UK or France or especially the Netherlands are almost not comparable to countries like Slovenia or Bulgaria. A good result would be that we could identify major areas for research and major areas of development to at least give a basic kind of support to cancer patients."

Value for money

It is critical to show that rehabilitation is good value for money, he adds. In Germany the cost of rehabilitation is covered by the pension fund, and cancer patients are the only ones who are entitled to draw on this even if they are retired – something that has recently generated a heated debate. "We have about 1 million rehabilitation patients for different kinds of diseases and about 18% of those – 100,000 to 180,000 people – are cancer patients. How can we justify this money?"

Garami, from Semmelweis University, Budapest, says that, despite the difficulties, the EUROCHIP initiative is crucial. "In the European Union we do not have a general rehabilitation system and we do not even provide a definition for rehabilitation. A major part of the national growth is going to oncology treatment, and rehabilitation is required to get the benefit, which means we have to get patients back in the work field or help them to get a normal life.

"Health services should offer in different countries different kinds of possibilities, but definitely they should offer basic treatment, such as physical rehabilitation, to help people return to work or even to a basic social life or emotional life.

"In major countries of the EU they do not have the right to rehabilitation. When active treatment is finished the patient is left alone."

With Europe in financial crisis, 'softer' areas of treatment and care are particularly vulnerable to cutbacks. Although it was not so obvious when the group was assembled, one key outcome might be to create a climate where the rehabilitation needs of patients diagnosed with cancer are seen as equally legitimate as the need for curative forms of treatment.