

# Dying for a lack of compassion?

➔ Anna Wagstaff

For dying cancer patients who have run out of therapeutic options, getting hold of drugs that are still in trials can offer them a last throw of the dice. Yet many find the system for getting early access to drugs, for so-called ‘compassionate use’, is beset by obstacles and delays. They want a greater sense of urgency... and a greater say.

**I**n June this year, the Life Raft Group – an advocacy organisation for patients with GIST – celebrated its 5th anniversary by looking back on its achievements and taking stock of how far knowledge about this relatively rare cancer and its treatment has progressed.

An anniversary newsletter carried articles on the 10 research groups that Life Raft is funding and on interesting findings from their own surveillance programme, in which 820 Life Raft members to date have agreed to submit details of their diagnosis, treatments and responses. Another piece offered an overview of current knowledge of the various mutations in GIST, looking at how these affect resistance to different therapies and discussing the value of trialling combination regimens.

This patient group is putting enormous work into getting to grips with the science behind their disease and co-operating with and contributing to the research effort that is helping keep them alive. However, in an upbeat anniversary publication, one article stands out because of its tone of exasperation and sadness. Written by executive director

Norman Scherzer, it talks about the Life Raft members who are dying without getting a chance to try the new therapies that everyone is talking about, even though they are available for clinical trials.

He picks out for special mention two patients who had stopped responding to imatinib (Glivec). One was seeking urgent access to sunitinib (now marketed as Sutent); the other had already tried and failed on sunitinib and wanted to try dasatinib (now marketed as Sprycel). Both drugs have since been approved for patients who have failed on Glivec (Sutent for GIST, Sprycel for chronic myeloid leukaemia), but even then, before approval, some information was known about the drugs, and the patient community had been following them closely since before they entered human trials. Reports received from researchers and via the Life Raft network looked encouraging.

One of these patients had voluntarily come off a trial for sunitinib, on the mistaken belief that the drug was causing unacceptable side-effects. When he found out he had been on placebo, and the symptoms were due to the progression

of his disease, he applied to rejoin the trial, but was refused. In the case of the second patient, the only trial within conceivable reach had completed enrolment. With the help of the Life Raft Group, both patients tried to get hold of the drug outside of the trial, on a so-called ‘compassionate use’ basis. But a combination of obstacles in getting hold of the drug and agreement for it to be administered outside the trials proved insurmountable.

“What could justify not getting a drug to a dying patient in a reasonable period of time, say a few hours or at most a few days?” asks Scherzer, who has fought endless battles with various parties to secure access to patients like these. “There is a feeling of helplessness as patients and caregivers try to navigate this institutional landscape to stay alive. It is easy to believe that this system was just not designed to meet the urgent needs of dying cancer patients.”

This is true. The system governing access to drugs is designed primarily to ensure that when a new drug enters the market there is strong evidence available on its efficacy and safety, so that doctors

and patients can make informed choices. If investigative drugs are widely available outside clinical trials, patients may have less incentive to enrol in a trial, which could make it harder to gather that evidence. The system is also designed to protect patients from exploitation by those offering false hope or even potentially harmful therapies. Dying cancer patients are particularly vulnerable, as has most recently been demonstrated by the scramble to get access to DCA (dichloroacetic acid), an acid that has shown promising anti-cancer activity in animals, but is available on the market only in forms not suitable for human use (see Do-it-yourself Chemotherapy Access, p 38).

### COMPASSIONATE USE

Within this system, the urgent needs of dying cancer patients are recognised by provisions covering 'compassionate use' – any authorised use, outside of clinical trials, of an investigative drug (i.e. under study but not yet approved). Within the EU, where cancer drug approval is centralised in the hands of the European Medicines Agency (EMA), Article 83 (1) of Regulation (EC) No. 726/2004 gives Member States the right to make certain categories of drugs available for compassionate use. How they do this – if at all – is up to them.

Many Member States have provisions for expanded access programmes (EAPs). These cover groups of patients with a speci-

fied indication, and tend to follow the same protocol as the relevant clinical trial. Their primary purpose is to widen the group of patients who can get access to the drug. Not all companies seek to set up EAPs, and those that do, will only do it for some of their drugs. Programmes tend to be set up once a phase III trial has recruited its full complement of patients, or in countries where no clinical trial is running or, possibly, for patients who are ineligible to join the trial. Such programmes can be used to gather additional information about the drug.

Pressure to set up expanded access schemes is particularly great where a drug is for patients who have few other therapeutic options – and, of course, where it has shown great efficacy in trials. Imatinib was a classic case, given to more than 7,000 patients through an expanded access scheme following dramatic results in phase II trials.

Even though not all EU countries have provisions for running EAPs, it should still be possible to apply for access to an investigational drug for compassionate use on a 'named-patient' basis. This usually requires a patient's physician to contact the company with a request that they supply the drug to their named patient. If the company agrees – and it is a big if – the physician can then apply to their national regulatory body for the go-ahead. They often also need permission from an ethics committee or their local health board before



“There is a feeling of helplessness as patients try to navigate this institutional landscape to stay alive”

they are allowed to administer a drug whose safety and efficacy has not been proven. In most countries, patients can also import unapproved drugs for their own use so long as the drug has been approved in some other country.

Differences between the systems operating across the EU affect the likelihood of an expanded access programme being set up or a given patient getting access on a named-patient basis. In some countries, all drugs supplied for compas-

sionate use have to be paid for by the manufacturer. In others the company may make a charge to cover administrative costs, and in some cases the charge can include cost of production, and even a small element of research and development costs.

In some countries, getting agreement for compassionate use can be very complex and time-consuming, involving bundles of paperwork and discussion at various levels. Others try to keep it simple.

## OBSTACLES

Patients face three main obstacles in their quest to “navigate through this institutional landscape”. First they have to find out what drugs are being trialled – or are about to enter trials – that might be relevant to their condition.

There is no legal obligation on companies to make this information public, and even when they do, the information can be hard to find, as Europe has no equivalent to the publicly accessible American clinical trials registry [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

The WHO is trying to establish a single clinical trials registry platform (see A Trial of Strength, *Cancer World* 11, Jan–Feb 2006), but the industry is resisting demands that they register phase I and II trials quickly enough and with sufficient detail to be of use to patients in urgent need.

In the absence of such a formal system of disclosure, some patient advocacy groups have become adept at picking up this sort of information – for instance by attending the professional conferences, and building relations with researchers from the clinical side and from the industry. Once in the hands of a motivated patient, the information spreads like wildfire via the web – but only to patients who know where to look.

The second obstacle is regulators, ethics committees or hospital boards who don’t want to OK the use of a drug when they feel they have too little evidence to evaluate whether it is more likely to help or harm the patient. This is an attitude that has baffled and infuriated dying cancer patients in equal measure. Today’s drugs, they argue, are designed to work on specific targets in a specific way, and a great deal is known about every compound long before it reaches human trials. If there is scientific rationale for believing that a drug could conceivably be of benefit, and if that drug is perceived to be safe enough for a

## Compassionate use

Compassionate use schemes are a way to give patients access to investigational drugs before they have been given marketing approval. They take two basic forms:

**Expanded access programmes** (EAPs), which are open to groups of patients providing they meet specific requirements regarding the type and stage of disease

**Named-patient programmes**, where access is negotiated on a patient by patient basis

In most countries it is also possible to import a product approved in another country, e.g. the US, for personal use

The rules covering compassionate use vary across Europe:

### France allows:

- Temporary named use (ATU) – for an individual patient
- Cohort ATU for a group of patients that are treated according to a protocol (expanded access programme)

### Germany allows:

- Named-patient sales of products that are approved in another country
- Named-patient programme

### Italy allows:

- Named-patient programme for products approved in another country or that have completed phase II trials
- Importation of a product approved in another country for personal use

### The UK allows:

- Open-label clinical trials (in which the doctor and patient knows what treatment is being given)
- Importation of product approved in another country for personal use
- Supply of drug on a named-patient basis

Source: A guide to cancer drug development and regulation, AstraZeneca 2006  
[www.cancerline.com/gUserFiles/Regulatory\\_Guide\\_Contents.pdf](http://www.cancerline.com/gUserFiles/Regulatory_Guide_Contents.pdf)

phase I or phase II trial, then patients who have run out of other options and are running out of time, should be given the chance to try it. As one of the patients who campaigned for early access to Glivec put it: “Novartis talks about the safety angle, but long-term side-effects mean nothing to me. If I don’t have treatment the only long-term effect for me is death”

The third major obstacle is getting agreement from the manufacturer to supply it. The company’s priority is to get their drug through clinical trials and onto the market as quickly and efficiently as they can, and they may fear that patients won’t join the trial if they can access the product another way. Companies may also be reluctant to hand out compounds that have not been well evaluated, for use outside the closely monitored and controlled setting of a clinical trial. Even if patients sign a waiver, confidence in the drug might be undermined before it has the chance to prove itself, if its first widespread use is in the sickest patients who are likely to have the most severe co-morbidities and may be the least likely to respond.

The biggest problem for companies lies in the cost and logistics of manufacturing a drug for widespread compassionate use. Early clinical trials need enough drugs for only a few hundred patients, which can usually be produced with basic laboratory facilities. Once thousands of patients are involved, however, major investment in production capacity may be required – something companies are understandably reluctant to do before they are certain their drug will get marketing approval.

In a book about the development of

## MARTI'S STORY



Marti Nelson discovered she had breast cancer at the age of 33. It was an aggressive cancer that was given the full treatment: mastectomy, chemotherapy and radiation. Seven years later the cancer had spread to her bones, liver and lung, but by that time a new drug was in trials that Nelson – herself a physician – believed could help her. This was 1994, the new drug was the HER2-neu monoclonal antibody that would eventually become Herceptin (trastuzumab) and it was being developed by Genentech, who were based nearby, in San Francisco. Nelson asked to be allowed to try the drug. Genentech refused, and Nelson died at the end of that year.

Nelson had long been active as a breast cancer advocate, but the big patient voice in San Francisco at the time came from the AIDS community, who were beginning to make progress in their own battle to get companies to give dying patients early access to drugs in development. Why couldn’t Genentech do the same for a breast cancer patient? is a question Nelson had asked. The AIDS activists rallied to support. The following year, when another breast cancer patient advocate, Barbara Moulton, called on Genentech for access to the drug, AIDS and breast cancer patients joined forces and organised lively protests outside the company’s headquarters.

Genentech argued that if they gave the drug at that stage in development, they would have to track the patients’ progress, which would be time-consuming and expensive. They also talked about the costs of production. “We’re... talking about a drug made through biotechnology, genetic engineering, which is difficult to make and expensive,” a spokeswoman said.

Moulton, like Nelson, died before being given the chance to try the HER2-neu antibody, but less than a week after her death Genentech announced it would start an expanded access programme.

“I think that any company that experiments on human beings has the responsibility to at least provide some drugs to people who have no other hope,” said Nelson’s husband Bob Erwin. “To say, ‘We’re just going to let you die until we can market this drug and make our profits’ – that’s just morally wrong.”

He now helps run the Marti Nelson Foundation/Cancer Action Now, which campaigns for more and better compassionate use schemes. Their website [www.canceractionnow.org](http://www.canceractionnow.org) provides very helpful advice to patients seeking access to experimental drugs.

“Long-term side-effects mean nothing to me. Without treatment the only long-term effect for me is death”



Glivec – *Magic cancer bullet* – Daniel Vasella, the Novartis CEO, talks about the huge gamble he took when he decided to invest in large-scale production facilities, “providing tons of Glivec active substance and millions of capsules instead of just kilogrammes and thousands of capsules.”

### UNFAIR

What this means for dying cancer patients is that, very often, even when companies do agree to supply the investigational drug outside of a clinical trial, only some of the patients seeking access get it – depending on where they live and who is their doctor.

The growth of Internet patient networks, where patients can swap stories about what they are on and seek tips about how to get hold of potential new options, has brought to light the great disparities in the time it takes for cancer patients with very urgent needs to access investigational drugs.

In a submission to an EMEA consultation on compassionate use, Eurordis, a European advocacy group for patients with rare diseases, painted the following picture. Companies sometimes restrict compassionate use programmes to centres that agree to run their regulatory trials, “as a gift to investigators”. Some companies only open programmes in Member States where they can levy a charge. Where product supply is limited, some companies distribute the drug on a first come, first served basis, which favours the best informed and those closest to the participating treatment centres or most able to travel. Other compassionate use programmes recruit at the sole discretion of

## EMEA guideline on compassionate use

### Eligibility

The Guideline defines eligibility for compassionate use programmes as patients with “A chronically or seriously debilitating disease, or a life threatening disease ... who cannot be treated satisfactorily by an authorised medicinal product”.

A key stipulation is that “patients should always be considered for inclusion in a clinical trial before being offered compassionate use programmes.”

### Level of evidence

In considering whether a drug should be made available for compassionate use, EMEA will consider “promising early data observed in exploratory trials (e.g. uncontrolled phase II trials)”.

### How triggered?

EMEA may offer an opinion provided one Member State has asked for such an opinion, or if two Member States have notified EMEA that they are seeking to set up compassionate use schemes.

*The full text can be found at [www.emea.europa.eu/pdfs/human/euleg/2717006enfin.pdf](http://www.emea.europa.eu/pdfs/human/euleg/2717006enfin.pdf)*

physicians. Ethics committees have been known to advise setting up lotteries or other random procedures for selecting patients, rather than prioritising those in most urgent need.

### EMEA GUIDELINES

European patient advocacy groups were hopeful that this inequity would be addressed this year, when EMEA drew up its first Guideline on Compassionate Use of Medical Products, which aimed to “facilitate and improve the access of patients in the European Union to compassionate use programmes”. EMEA said that it would “favour a common approach regarding the conditions of use, the conditions for distribution and the patients targeted for the compassionate use of unauthorised new medicinal products.”

In the event, the Guideline, published this July, fell far short of patient community aspirations. It provides a legal basis for EMEA to issue ‘an opinion’

on compassionate use of an investigational drug, which would cover conditions of use (dosage, how to administer and use safely), conditions for distribution (whether subjected to special or restricted medical prescription) and target patient groups.

A disappointed Eurordis criticised the Guideline as “a missed opportunity” to tackle key inequities in the supply of drugs for compassionate use. Eurordis wants EMEA’s opinion on ‘conditions of distribution’ to cover how much drug should be available in how many Member States, and believes that EMEA would have a better opportunity of achieving a fair compassionate use programme if it were to discuss conditions for distribution collectively with the manufacturers and all Member States together. This, they argue, would prevent companies from cherry-picking where they distribute investigational drugs and under what conditions. “25 [Member States]

# Eurordis criticised the EMEA Guideline as ‘a missed opportunity’ to tackle key inequities

together are in a better position to negotiate ... key aspects of a compassionate use programme than each of them separately."

EMA acknowledges concerns "in respect of differential supply to Member States markets of compassionate use products", but says that its powers are restricted to scientific opinion and do not extend to market supply.

The industry, in contrast, feels EMA is being far too bold, and a number of industry bodies indicate unease at the prospect of EMA issuing opinions about compassionate use before establishing whether the manufacturer can or will supply the drug. The European Federation of Pharmaceutical Industries Associations (EFPIA) says: "To generate publicly available ... recommendations for compassionate use in a situation where the applicant is not in a position to satisfy request for the drug would be unethical."

Under the guideline, EMA can issue an opinion on compassionate use if one Member State requests it, or if two or more Member States notify EMA that they are looking to set up a compassionate use programme. The industry presumably fears that, once an opinion is issued, patients and doctors in every EU country will use it to put pressure on the company to supply the drug. This is probably exactly what will happen – but as Eurordis points out, the leverage that patients and their doctors have lobbying country by country is far smaller than it would be if they all sat around the same table.

## THE AIDS EXPERIENCE

Ten years ago, Europe's AIDS patients reached a very similar conclusion. They set up the European Community Advisory Board in 1997 to give them a platform from which they could influence drug development from the earliest stage of designing a trial, through to post-

approval monitoring of adverse side-effects. Early access for all European patients was a key issue for them.

ECAB was based on the concept of the community advisory boards that pharmaceutical companies set up to get advice and feedback from patients, but it had two crucial differences. It is part of an independent patient organisation, the European AIDS Treatment Group, which means that patients set their own

agenda, and it gives a single voice to AIDS patients throughout Europe, which ensures that pharmaceutical companies listen to them. The board is composed of 20–30 patients who have developed expertise in the area of research and trials. They meet several times a year to discuss clinical trials and developments in the pipeline with pharmaceutical companies, and to organise training for new members.

## ABIGAIL'S STORY



Abigail Burroughs died in 2003 at the age of 21 from a head and neck cancer, at a time when the first epidermal growth factor receptor (EGFR) inhibitors were in early clinical trials. Gefitinib (Iressa) was being tested by AstraZeneca for use in non-small-cell lung cancer, and cetuximab (Erbix), developed by ImClone, was in trials for colorectal cancer. Abigail's tumour was rich in epidermal growth factor receptors, and her oncologist was very hopeful that it might respond to one of the EGFR inhibitors. Neither company, however, was willing to let her try drugs that were very experimental and were being trialled for use in other settings. In the words of her doctor, "she had the right cells in the wrong place".

After failing to show strong proof of efficacy, Iressa was refused marketing approval by EMA. Erbix, however, has been approved not only to treat colorectal cancer, but also subsequently for squamous cell head and neck cancer.

Following Abigail's death, her father Frank Burroughs started the Abigail Alliance to help patients like his daughter get access to drugs that might help them. The Alliance brought a law suit against the US regulator, the FDA, to try to remove all regulatory controls over dying patients seeking access to investigational drugs, on the ground that they operate "as a death sentence... in violation of the guarantee in the Fifth Amendment of the US Constitution against deprivation of life without due process".

This was rejected by an Appeals Court in August 2007. The Alliance is now pinning its hopes on changing the law through an 'Access Act', to allow companies to seek what the Alliance has called "Tier 1 approval" to market drugs to certain categories of patients with life-threatening diseases, on the basis of minimal evidence of clinical efficacy – in effect a small number of case reports. Some large and well-established patient advocacy bodies, including the US National Breast Cancer Coalition and the US National Coalition for Cancer Survivorship, are opposing the Act, arguing that it would result in the market becoming awash with drugs for which hard scientific data will never be collected.

Simon Collins has been a member of ECAB since it started, and co-chair for two years, during which time he has been involved in negotiating numerous expanded access programmes. Pressure from patients – and from doctors – he says, is essential. “If there was no pressure from patients, there wouldn’t be any EAPs. It is driven by patient demand and many

doctors as well.” He points out, however, that not all doctors are prepared to use earlier access for their patients, sometimes for bureaucratic reasons, “With all the work that we do as advocates trying to get these programmes going, it is heartbreaking to see the blocks we get from doctors saying: ‘Oh no, I don’t want to do all that paperwork. I’d rather wait for approval.’”

### ANDY’S STORY



Andy Giusti is 42 years old and ‘in excellent health’ – except for the stage IV colorectal cancer he had diagnosed two and a half years ago, which will kill him if he doesn’t find a therapy that works. The clock is ticking.

A biotechnology research scientist by profession, Giusti has been following developments in cancer therapies to identify something that might help him. It was almost two years ago, at a research meeting on colorectal cancer, that he first came across a DNA vaccine, Trovax, which is designed to work in all solid tumours where the 5T4 tumour antigen is present. Early results of a phase II trial using the vaccine in combination with FOLFOX and FOLFIRI (standard treatment for stage IV colorectal cancer) were presented, and looked promising.

He contacted the manufacturer – a small but well-established biotechnology company in the UK – to see whether there were any new clinical trials planned that he might be eligible for, and ask about their policy on compassionate use. The answer came back that there were no new trials planned in colorectal cancer, and that all of the vaccine they were manufacturing was being used for other trials – no compassionate use programme.

“Two years have now elapsed,” says Giusti. “I have seen in the news that sanofi-aventis is now partnering with Oxford BioMedica to bring Trovax forward into a phase III trial for colorectal cancer. In this time extensive safety data has been generated using this vaccine, and indications are that it still shows promise for metastatic colorectal cancer patients. However, I have now been treated with all of the chemotherapy/biologic treatments that are currently approved. Unfortunately, I still have visible disease, and because of this extensive treatment history I am not likely to meet the inclusion criteria for this upcoming phase III trial.”

An active patient advocate, Giusti says he is well aware of the complex issues surrounding access to experimental drugs, but he believes companies have a duty to make an effort to help patients like himself, who have run out of options, particularly if the drug is already cleared for phase III trials and a major pharmaceutical company is involved. “Our initial efforts have not met with much success,” says Giusti, “but I am hopeful that we will ultimately reach an individual at one of these companies that will open a productive dialogue about access to Trovax via compassionate use.”

However, he agrees with Eurordis that manufacturer supply problems are the most common obstacle to early access. “The major block is the pace the company wants to run this programme – how soon they plan to scale up their production line sufficiently to have an expanded access programme. As soon as they have efficacy data – some of that comes from phase II – and a reasonable safety indication, we say the company should plan for scaling up the expanded access programme before they start phase III studies. We tell them that they should be planning the scale up much earlier in their production programme.”

The great advantage of operating at a European level is the ability to address in a single forum issues that are common to patients throughout the 27 countries of the EU. When ECAB asks companies to scale up an expanded access programme, they ask for that programme to run all over Europe, and give feedback to the company when there are unacceptable delays. “Some countries can be very slow at getting these EAPs up and running. You can agree something with the central company, but then the Portuguese or Spanish ECAB member, for instance, may come back and say, ‘Well we phoned Roche (or Merck, or whatever) locally, and they don’t know anything about it.’ It makes the company aware of problems with their affiliates.”

### LET’S GO!

What ECAB has done for one section of Europe’s patients is to give them a voice at the table. And what patients bring to that table, above all, says Life Raft’s Scherzer, is a sense of urgency. “It’s always been surprising to me that the world of cancer treatment and experimental cancer treatment seems to lack a sense of urgency. I worked for many years in public health, including at the Centres of Disease Control – that world was exactly the opposite. It is a world of





LESLIE MULKEY

Delay = death. American patient advocates from the Abigail Alliance, the Cancer Cure Coalition, A Right To Live (a prostate cancer advocacy group) and the Sarcoma Foundation of America took their message to the FDA's headquarters in Rockville, Maryland, September 18th

great urgency. To some extent, I am terribly fortunate or unfortunate – I had no training for this culture and I bring to it a completely different set of values. Let's go, let's move, what's the problem? That attitude sometimes helps."

He and his Life Raft colleagues have helped countless patients seek compassionate access to investigative drugs – including drugs that are still in, or about to start, phase I trials. It is a constant search for ways to influence a system in which patients have never been invited to play a role. The Life Raft monthly newsletter is sent to as many researchers and executives as patients, and the group has a very active website. "We have the capacity to state our position. We also have a very good relationship with the media. So that gives us a bit of leverage in imposing ourselves on the system."

On one memorable occasion,

Scherzer informed the head of a top hospital in Europe that he would be 'named and shamed' in their newsletter if he did not speed up the process of setting up a clinical trial, given the lives that were at stake. Scherzer was threatened with a libel suit for his trouble, but the clinical trial started the very next morning!

Life Raft is not always so successful, and after years of firefighting on behalf of dying patients, Scherzer is beginning to question why patients and patient advocates should be reduced to lobbying, cajoling or threatening from the margins.

"My philosophy is changing and I have adopted the mantra that the European Cancer Patient Coalition has developed, which is 'Nothing About Us Without Us'. I used to think it would really be something if they would even let us in the room. Then I thought, I'd like

a seat at the table and I would like it to be one of those decision-making seats. And now I have adopted probably the most controversial point of view. I think I should be sitting at the head of the table running the meeting, because I am the only one in the room for whom the needs of the patient are in fact the first and paramount priority."

Controversial with some perhaps, but this was of course precisely what the European AIDS patients did when they set up ECAB, which has served them well. And given that EMEA has now made it clear its influence over compassionate use will extend no further than presenting an opinion, Europe's cancer patients could find such a table just the forum to exert pressure for compassionate use schemes to be set up early and equitably across all Member States.

"I should be at the head of the table ... I am the only one for whom the needs of the patient are paramount"