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

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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

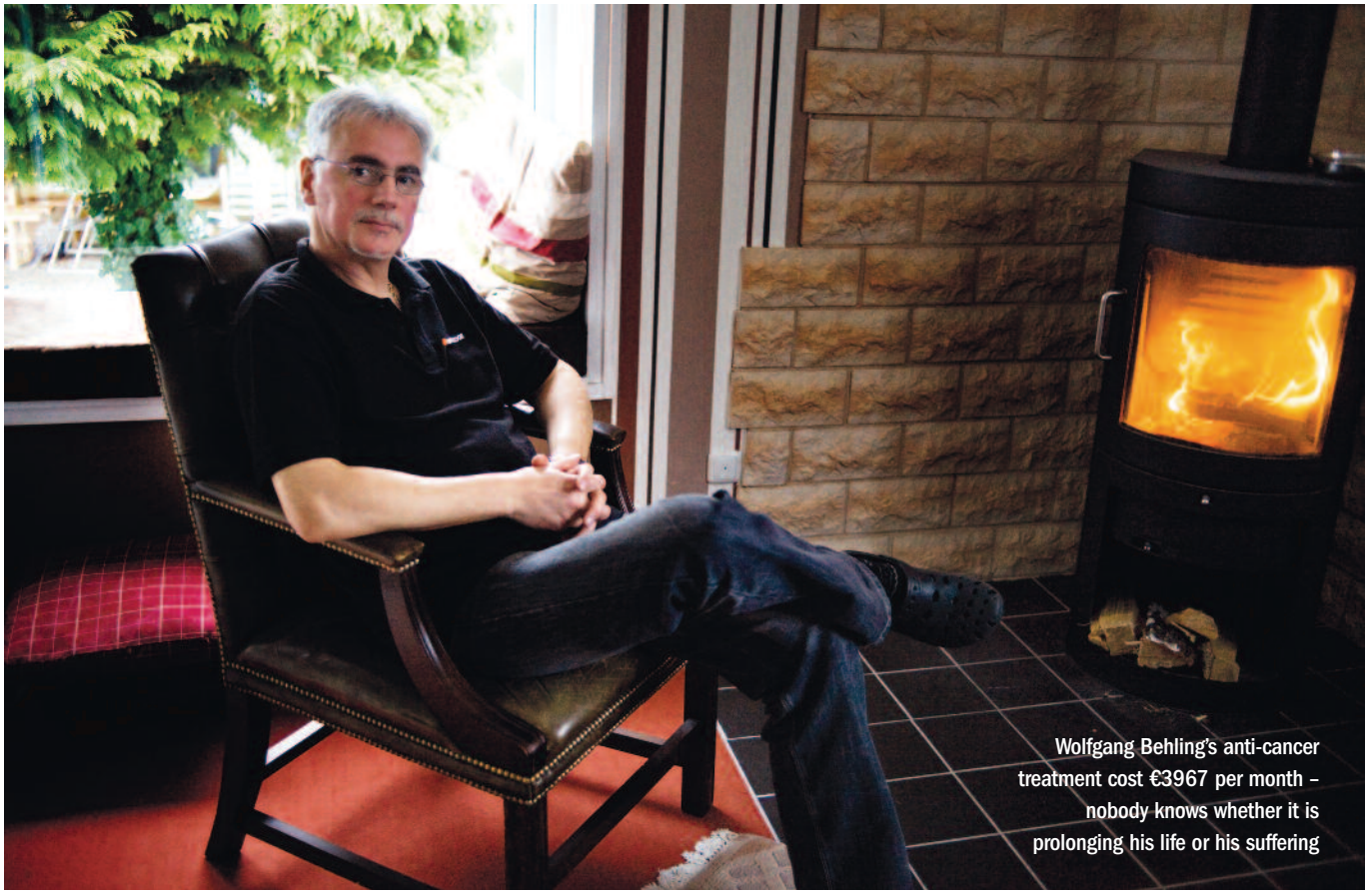
Oncologist Ludwig from Berlin is not the only doctor criticising this industry. He is part of a small but growing group of experienced cancer doctors who are able to speak out more freely than others, because they are independent from the pharmaceutical industry – for example, they don't take fees from 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?

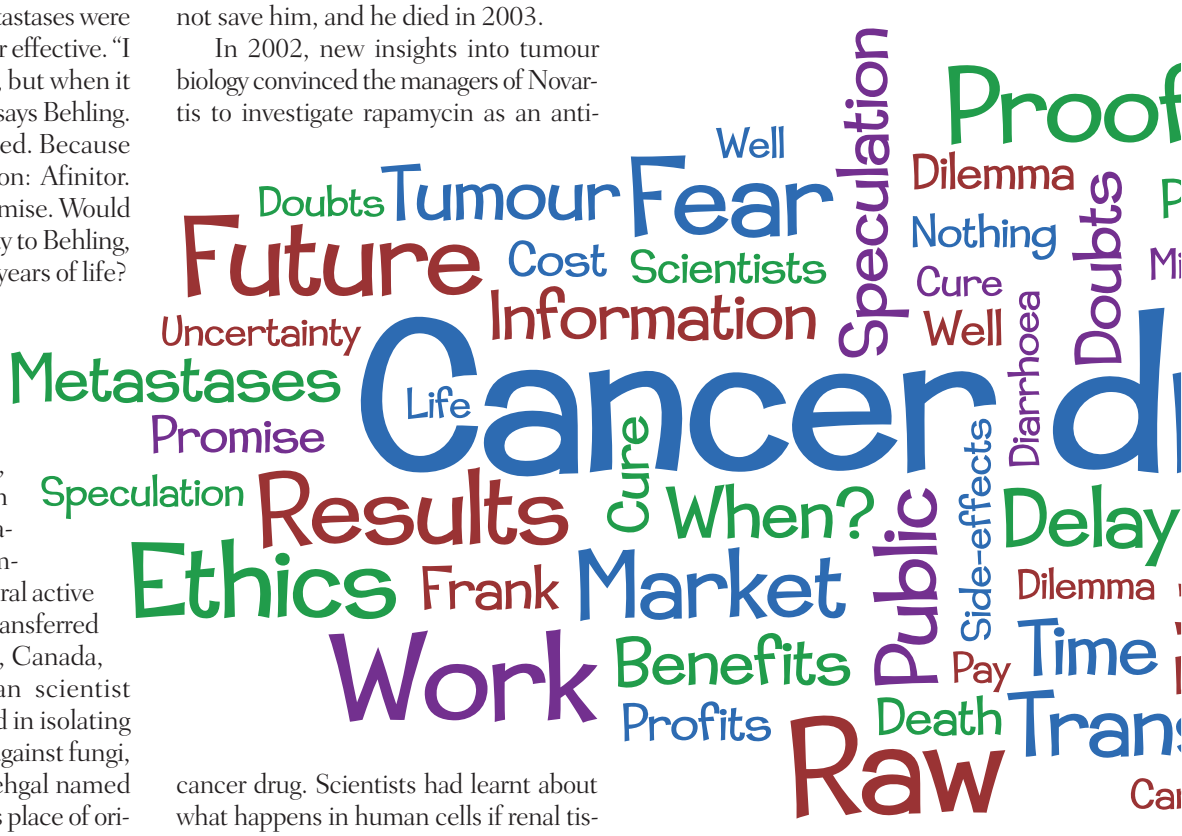
The back story

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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