The 'no miracle cure' story

The story of step-by-step progress, with occasional leaps forward and frequent setbacks, is not one the media enjoys telling. But it does need to be told if patients and society are to learn to live with cancer as a chronic disease. **Linda Geddes** received a Best Cancer Reporter Award for her article *Living with the Enemy*, which made an easy read of a complex story, and is reprinted below.

At first the doctors put it down to the fact that she was 22 weeks pregnant with her second child. But when the lump in Claire Young's left breast didn't go away, she had a scan that showed it was cancer. The pregnancy meant Young couldn't be put on highly toxic chemotherapy, so surgeons removed the breast. At 38 weeks, she was induced and gave birth to a healthy boy.

That was in 2004. "Although it was a fairly aggressive tumour, they were fairly confident that they had got all of it out," Young says. As a precaution, she was started on epirubicin and cyclophosphamide – standard chemotherapy for breast cancer – and given radiotherapy. Because her tumour cells had tested positive for oestrogen receptors, she was also put on tamoxifen, a drug that blocks the supply of the female sex hormone that triggers some breast tumours to grow.

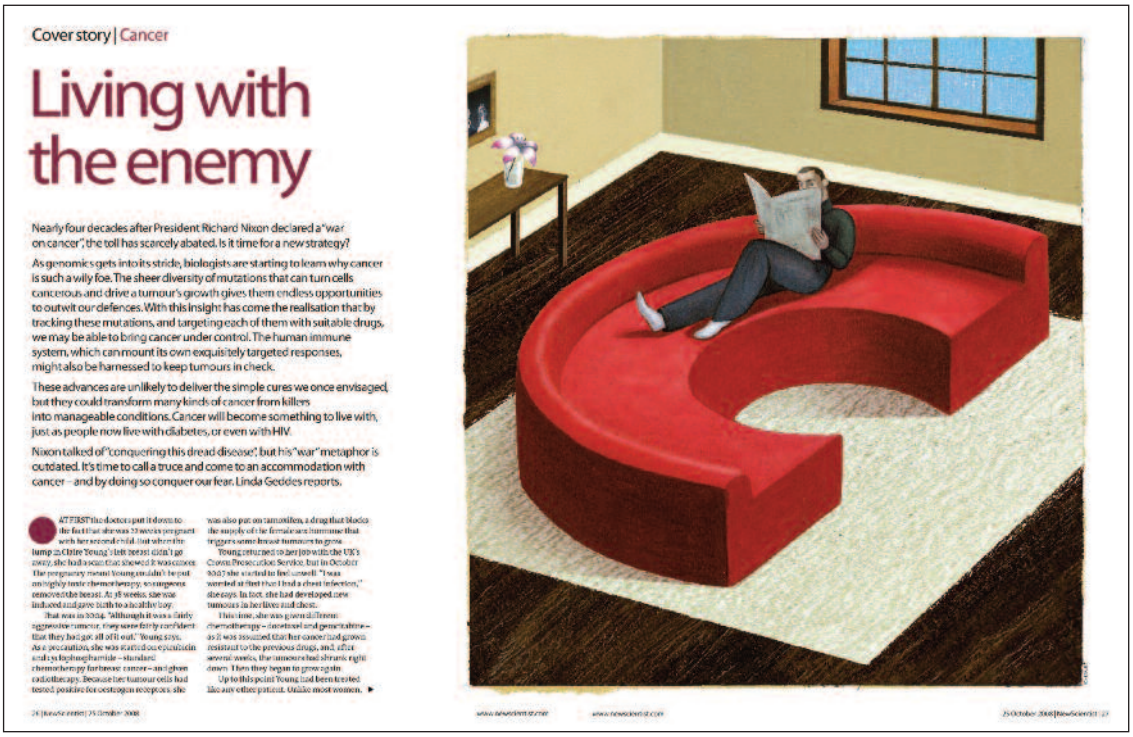
Young returned to her job with the UK's Crown Prosecution Service, but in October 2007 she started to feel unwell. "I was worried at first that I had a chest infection," she says. In fact, she had developed new tumours in her liver and chest.

This time, she was given different chemotherapy – docetaxel and gemcitabine – as it was assumed that her cancer had grown resistant to the previous drugs, and, after several weeks, the tumours had shrunk right down. Then they began to grow again.

Up to this point Young had been treated like any other patient. Unlike most women, though, she tested positive for a mutation in

Linda Geddes

NewScientist



Cover story | Cancer

Living with the enemy

Nearly four decades after President Richard Nixon declared a "war on cancer", the toll has scarcely abated. Is it time for a new strategy?

As genomics gets into its stride, biologists are starting to learn why cancer is such a wily foe. The sheer diversity of mutations that can turn cells cancerous and drive a tumour's growth gives them endless opportunities to outwit our defences. With this insight has come the realisation that by tracking these mutations, and targeting each of them with suitable drugs, we may be able to bring cancer under control. The human immune system, which can mount its own exquisitely targeted responses, might also be harnessed to keep tumours in check.

These advances are unlikely to deliver the simple cures we once envisaged, but they could transform many kinds of cancer from killers into manageable conditions. Cancer will become something to live with, just as people now live with diabetes, or even with HIV.

Nixon talked of "conquering this dread disease", but his "war" metaphor is outdated. It's time to call a truce and come to an accommodation with cancer – and by doing so conquer our fear. Linda Geddes reports.

AT FIRST the doctors put it down to the fact that she was 33 weeks pregnant with her second child. But when the lump in Chitte Young's left breast didn't go away, she had a scan that showed it was cancer. The pregnancy meant Young couldn't be put on highly toxic chemotherapy, so surgeons removed the breast. At 38 weeks, she was induced and gave birth to a healthy boy.

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An uneasy truce. Writer Linda Geddes suggests the time may have come to move on from the terminology of fighting a war against cancer and look instead towards the HIV scenario of long-term survival through tracking and targeting mutations as they arise

the gene BRCA2, which indicated that her cancer was a rare hereditary form. She could either try another round of chemotherapy with different drugs or enrol on a clinical trial for a new drug called a PARP inhibitor, which should be particularly effective in women with mutant BRCA2. "We hope that by using the PARP inhibitor we can offer more targeted treatment," says Ruth Plummer of Newcastle University, UK, who is leading the trial.

Cases like Young's are part of a trend that looks likely to transform the prospects of cancer patients. In the genomics era, biologists are amassing information about the molecular pathways that drive cancer, and this is leading them to question the traditional method of classifying tumours according to where in the body they appear. Instead, researchers are realising that what matters are the particular mutations that make the cells in a tumour grow in an uncontrolled fashion. Two patients with cancers in completely different tissues, but triggered by the same mutation, may have more in common with each other than people with

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tumours in the same organ but caused by different molecular mechanisms. Conversely, two patients with superficially the same type of cancer may have very different prognoses, depending on the underlying mutations.

Once you throw away the notion of cancer as an anatomically defined disease and focus on these molecular abnormalities, treatment becomes a different ball game. Conventional chemotherapy and radiotherapy work by being especially toxic to dividing cells. While these treatments damage the fast-growing tumour cells, they also exact a terrible toll elsewhere in the body. "We're looking at getting away from that model and understanding the changes that occur in cancer that differentiate it from normal cells," says Rameen Beroukhim of the Dana-Farber Cancer Institute in Boston, Massachusetts. "Once you know this, you can come up with drugs that specifically target those changes."

This approach has convinced many oncologists that they will be able to transform cancer from a lethal disease into a chronic condition that people may be able to live with almost indefinitely. It won't be easy. Treatments will probably require cocktails of targeted drugs that will have to be adjusted as tumours mutate. In theory, though, these therapies should work much better than those available today, and have fewer side-effects. "More targeted therapies will convert a lot more cancers from being short-term death sentences to manageable problems," says Beroukhim.

The obvious parallel is with HIV, where a cocktail of anti-retroviral drugs can slow down the replication of the virus, enabling people to live with the infection until old age. If they develop resistance to one drug, they are moved to a different one. "HIV was turned from a lethal disease into a chronic condition, and we hope to do the same thing with cancer," says Beroukhim.

Progress in understanding the molecular diversity of breast cancer is providing a hint of the possibilities. In the mid-1990s, geneticists discovered BRCA1 and BRCA2, two genes that between them are responsible for just over half of all hereditary forms of breast cancer. The genes encode proteins involved in DNA repair, so when they are defective, cells become more likely to accumulate cancer causing mutations.

The PARP inhibitor that Young is helping to test blocks an enzyme involved in a different DNA repair pathway. While it might sound odd to treat a disease by making the problem worse, the idea is that cells whose DNA repair pathways have been disrupted more thoroughly will be so crippled that they will die. So far, Young has responded well.

Inherited mutations account for only some 10% of breast cancers, so the biggest effort in breast cancer and other tumours is to identify the mutations that arise spontaneously in individual cells to make them turn cancerous. For instance, the International Cancer Genome Consortium (ICGC), set up in April 2008, aims to sequence the DNA from 25,000 individual tumours to document the mutations implicated in 50 of the most common cancers.

A huge diversity of mutations, of various different types, may be involved. They include single-letter changes to the genetic code, larger genetic deletions, insertions and duplications, and chromosomal rearrangements that can cause parts of different genes to become fused together. Chemical modifications to DNA, such as the addition or removal of methyl groups, can also affect the activity of individual genes.

Initial genomic studies on a form of brain cancer known as glioblastoma have already revealed that it is essentially two diseases with

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a different age of onset and pattern of survival, depending on whether a gene called IDH1 is mutated (*Science* 321:1807).

Clues that breast cancer is more than one disease arose from experience with tamoxifen, approved for use in 1977, as the drug works only in patients whose tumours carry receptors for the hormone oestrogen.

More than one disease

Since then, oncologists have discovered that 15%–25% of breast cancers are driven by mutations that cause cells to produce large amounts of a cell-surface receptor called HER2. This can be targeted with an antibody called trastuzumab, better known by its brand name Herceptin.

These advances are just the start. "Breast cancer is 10 diseases, or 15 – I don't think it's even clear how many – and there are multiple mechanisms and combinations of mutations that arise," says Joe Nevins, who studies the genomics of breast cancer at Duke University in Durham, North Carolina.

As the ICGC and related initiatives turn up more information about the individual mutations involved in different tumours from various parts of the body, they are likely to find that drugs currently used against one anatomical variety of cancer will find uses in subsets of patients with tumours that arise elsewhere. For example, last year a patient with the deadly skin cancer melanoma was treated with a drug called imatinib or Glivec (Gleevec in the US), generally used to treat leukaemia, after the cancer was found to have a mutation in the gene for a protein called c-kit, one of imatinib's targets (*JCO* 26:2046). "This patient had a near complete response," says William Sellers, global head of oncology with the drugs giant Novartis. "If you talk to a lot of melanoma doctors, I don't think they believe that melanoma is a treatable cancer."

Targeted drugs

Imatinib will not benefit everyone with melanoma – the mutation it targets is implicated in just 5% of cases – but its effectiveness in those instances suggests that greater use of molecular profiling could lead to improvements in patient survival even with the current crop of targeted drugs. "We've got a lot of drugs right now, but in most cases we don't use them very well," says Nevins.

The bewildering array of mutations involved in different forms of cancer means that many more targeted drugs will be needed. Even within one tumour, several different molecular pathways may be driving its growth. And cancer cells become more unstable over time, accumulating multiple mutations that further increase their chances of being able to resist drugs. "The malignant cell is a moving target," says Fran Balkwill of the Institute of Cancer at Barts and the London School of Medicine and Dentistry.

Then there is the problem of tracking genetic changes as they occur. Frequent biopsies may cause patients discomfort or worse – even if their tumours are accessible, which often they are not. With this in mind, Daniel Haber of the Massachusetts General Hospital

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Cancer Center in Charlestown has developed a way of analysing mutations in stray cancer cells that can be extracted from blood samples. His team recently showed that cells from some patients with non-small-cell lung cancer developed additional mutations in the gene for the epidermal growth factor receptor after being treated with gefitinib (Iressa), which blocks a cancer-causing pathway triggered by mutated forms of the receptor (*N Engl J Med* 359:366). By monitoring such changes doctors will get a better idea of when to change patients' drugs or add in extra ones to counter resistance.

Testing the array of new drugs that will be needed to tame tumours over long periods will require a change in the way clinical trials are designed. The traditional approach, in which drugs are tested in large groups of patients with the same anatomical variety of cancer, will no longer cut it. In future, recruits will have to be selected carefully, otherwise potentially valuable drugs may be needlessly written off. "We need to be genetically profiling patients as they enter, or even before they enter, the clinical trial," says Sellers.

Drugs will also need to be tested in combination, as bitter experience has shown that a single drug is unlikely to be enough. One way in which lung cancer cells can become resistant to gefitinib is by ramping up production of a protein called MET, which is involved in a related pathway. Combining gefitinib with a MET inhibitor might be one way of overcoming this resistance.

"Where we are now is that we have drugs that are transiently effective, but that tumours work around them as they develop," says Joe Gray, who studies the molecular causes of cancer at the Lawrence Berkeley National Laboratory in California. "As we understand the circuitry better, I think we'll be able to understand how to block the parallel pathways. Once we can do that, I believe we're headed in the direction of longer and longer patient survival."

There are plenty of obstacles ahead, however. One is the expense of therapies that rely on multiple treatments targeted to different molecular pathways. Another is the possibility that some therapies may turn out to be less targeted than was hoped. For example, when the drug sunitinib (Sutent) was given in combination with the antibody bevacizumab (Avastin), which inhibits the growth of blood vessels into a developing tumour, it caused anaemia. Why this happened nobody yet knows. "Whilst we have a very good rational basis for the design of new drugs, we have to stay open to the idea that these things work in quite different ways to what we might anticipate," says Peter Johnson, chief clinician with Cancer Research UK.

Still, researchers remain optimistic that targeted therapies will help to eliminate some of the more fearsome side-effects of cancer treatments. Claire Young has experienced some adverse effects from the PARP inhibitor, but they are a lot less debilitating than the nausea and hair loss that she experienced while on conventional chemotherapy. She realises that she may never be cancer-free. "Short of a miracle, I'm not expecting them to cure me," she says, and for now she is setting short-term targets. "We're hoping to go to Disney World in Florida in April."

That doesn't mean she is giving in to cancer. "I'll fight it hammer and tongs, and if there's something to try I'll give it a go." Her fight may help to pave the way for people to live with cancer into a ripe old age, rather than waging a futile war.

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