heart valve was introduced, but the early models were prone to thrombosis (clot formation) that impaired their function. To overcome this drawback, the design was modified in the late 1970s to reduce the possibility of clots.

The new device involved a disc held in place by two metal struts (supports), and many thousands of this new type of valve were implanted worldwide. Unfortunately, the structure of the valves was seriously flawed: one of the struts had a tendency to snap – a defect known as strut fracture – and this led to catastrophic and often fatal valve malfunction.

As it happened, strut fracture had been identified as a problem during pre-marketing tests of the device, but this was attributed to defective welding and the cause was not fully investigated. The US Food and Drug Administration (FDA) nevertheless accepted this explanation, along with the manufacturer's assurance that the lowered risk of valve thrombosis more than compensated for any risk of strut fracture. When the evidence of disastrous valve failure became only too apparent, the FDA eventually acted and forced the valve off the market in 1986, but not before hundreds of patients had died unnecessarily. Although product regulation systems have now improved to include better post-marketing patient monitoring and comprehensive patient registries, there is still a pressing need for greater transparency when new devices are introduced.[8]

TOO GOOD TO BE TRUE

Herceptin

Commercial companies are not alone in trumpeting the advantages of new treatments while down-playing drawbacks. Professional hype and enthusiastic media coverage can likewise promote benefits while ignoring potential downsides. And these downsides may include not only harmful side-effects but also diagnostic difficulties, as shown by events surrounding the breast cancer drug trastuzumab, better known by the trade name Herceptin (see also Chapter 3).

In early 2006, vociferous demands from coalitions of patients

and professionals, fuelled by the pharmaceutical industry and the mass media, led the UK National Health Service to provide Herceptin for patients with early breast cancer. 'Patient pester power' triumphed – Herceptin was presented as a wonder drug (see Chapter 11).

But at that time Herceptin had only been licensed for the treatment of metastatic (widespread) breast cancer and had not been sufficiently tested for early breast cancer. Indeed, the manufacturers had only just applied for a licence for it to be used to treat early stages of the disease in a very small subset of women – those who tested positive for a protein known as HER2. And only one in five women has this genetic profile. The difficulties and costs of accurately assessing whether a patient is HER2 positive, and the potential for being incorrectly diagnosed – and therefore treated – as a 'false positive', were seldom reported by an enthusiastic but uncritical press. Nor was it emphasized that at least four out of five patients with breast cancer are not HER2 positive.[9, 10, 11, 12]

It was not until later that year that the UK's National Institute for Health and Clinical Excellence (NICE) – the organization charged with looking at evidence impartially and issuing advice – was able to recommend Herceptin as a treatment option for women with HER2 positive early breast cancer. Even then, there was an important warning. Because of mounting evidence that Herceptin could have adverse effects on heart function, NICE recommended that doctors should assess heart function before prescribing the drug, and not offer it to women with various heart problems, ranging from angina to abnormal heart rhythms. NICE judged that caution was necessary because of short-term data about side-effects, some of them serious. Long-term outcomes, both beneficial and harmful, take time to emerge.[13]

Similar pressures for use of Herceptin were being applied in other countries too. In New Zealand, for example, patient advocacy groups, the press and the media, drug companies, and politicians all demanded that breast cancer patients should be prescribed Herceptin. New Zealand's Pharmaceutical Management Agency (PHARMAC), which functions much as NICE does in the UK, similarly reviewed the evidence for use

ON BEING SUCKED INTO A MAELSTROM

In 2006, a patient in the UK, who happened to be medically trained, found herself swept along by the Herceptin tide. She had been diagnosed with HER2 positive breast cancer the preceding year.

> 'Prior to my diagnosis, I had little knowledge of modern management of breast cancer and, like many patients, used online resources. The Breast Cancer Care website was running a campaign to make Herceptin available to all HER2 positive women and I signed up as I simply could not understand, from the data presented on the website and in the media, why such an effective agent should be denied to women who, if they relapsed, would receive it anyway. . . . I began to feel that if I did not receive this drug then I would have very little chance of surviving my cancer! I was also contacted by the Sun newspaper who were championing the Herceptin campaign and were interested in my story, as a doctor and a "cancer victim".
>
> At the completion of chemotherapy, I discussed Herceptin treatment with my Oncologist. He expressed concerns regarding the long-tem cardiac [heart] effects which had emerged in studies but had received very little attention on the website and from the media, especially when one considered that the drug was being given to otherwise healthy women. Also, more careful analysis of the "50% benefit" which had been widely quoted and fixed in my mind actually translated into a 4-5% benefit to me, which equally balanced the cardiac risk! So I elected not to receive the drug and will be happy with the decision even if my tumour recurs.
>
> This story illustrates how (even) a medically trained and usually rational woman becomes vulnerable when diagnosed with a potentially life threatening illness. . . . much of the information surrounding the use of Herceptin in early breast cancer was hype generated artificially by the media and industry, fuelled by individual cases such as mine.'

Cooper J. Herceptin (rapid response). *BMJ*. Posted 29 November 2006 at www.bmj.com.

of Herceptin in early breast cancer. In June 2007, based on its review, PHARMAC decided that it was appropriate for early breast cancer patients to receive nine weeks of Herceptin, to be given at the same time as other anti-cancer drugs, rather than one after another. This nine-week course was one of three regimens then being tried around the world. PHARMAC also decided to contribute funds to an international study designed to determine the ideal length of Herceptin treatment. However, in November 2008, the newly elected government ignored PHARMAC's evidence-based decision and announced funding for a 12-month course of the drug.[14]

Numerous uncertainties remain about Herceptin – for example, about when to prescribe the drug; how long to prescribe it for; whether long-term harms might outweigh the benefits for some women; and whether the drug delays or prevents the cancer returning. A further concern that has emerged is that Herceptin, when given in combination with other breast cancer drugs such as anthracylines and cyclophosphamide, may increase the risk of patients experiencing adverse heart effects from about four patients in a hundred to about 27 patients in a hundred.[15]

KEY POINTS

- Testing new treatments is necessary because new treatments are as likely to be worse as they are to be better than existing treatments
- Biased (unfair) tests of treatments can lead to patients suffering and dying
- The fact that a treatment has been licensed doesn't ensure that it is safe
- Side-effects of treatments often take time to appear
- Beneficial effects of treatments are often overplayed, and harmful effects downplayed