Herceptin and early breast cancer: a moment for caution

It is no surprise that patients with cancer, together with leading cancer charities, are calling for the faster approval of drugs they see as life saving. One UK charity, Cancer Bacup, has identified a "dossier of delay" in current procedures. The chief culprit in Britain is said to be the National Institute for Health and Clinical Excellence (NICE). The story is not so simple.

Under considerable political and media pressure, NICE and the Department of Health last week announced the launch of a rapid process for assessing new and potentially life-saving medicines. Five drugs have been targeted for fast-track: trastuzumab (Herceptin), docetaxel, and paclitaxel for breast cancer; rituximab for non-Hodgkin's lymphoma; and bortezomib for multiple myeloma. While these developments show commendable responsiveness to public concern, they must not be allowed to undermine NICE's hard-won and well-deserved reputation for independence and scientific rigour. Herceptin is a case in point.

In March, 2002, NICE recommended Herceptin for use in women with HER2-positive advanced breast cancer, either alone or in combination with paclitaxel. The process leading to this decision was criticised for taking too long. NICE justified its timing by pointing out the need for careful and thoughtful scrutiny of the available data by an independent advisory committee. NICE's principal concern was to provide reliable advice. Their spokeswoman noted that, "we felt it right that we allow the independent committee that advises NICE the time it needed to analyse and consider this evidence before they gave us their final advice". This view is surely correct. Whatever the sense of urgency, it is crucial that NICE resists pressure to make expedient decisions.

Three years on, a similar but even more intense debate surrounds the use of Herceptin for early breast cancer. Promising results were initially presented at this year's American Society of Clinical Oncology annual meeting. An immediate wave of demand for Herceptin grew, despite the fact that the drug was not only unlicensed for this indication but also that its manufacturer, Roche, had not even submitted data for the drug's approval. Some countries, such as France, bypassed their official approvals procedure to make Herceptin available. In October, these studies were finally reported in the *New England Journal of Medicine*. In an accompanying editorial, Dr Gabriel Hortobagyi described the results as "simply stunning" and "revolutionary". He even went so far as to say that Herceptin was "maybe even a cure" for breast cancer. Naturally this comment was picked up and repeated across the world, fuelling demand for rapid access to Herceptin. The excitement is premature.

The studies so far reported represent interim efficacy analyses. As Victor Montori and colleagues advised in last week's *JAMA*, such analyses may "show implausibly large treatment effects". They recommend that "clinicians should view the results of such trials with scepticism". The two *NEJM* reports use different dosing regimens, making comparisons and conclusions additionally more difficult. It is especially hard to tease apart the results because one of the papers combines results from two trials sponsored by Genentech. Although the "joint analysis was developed and analysed" by both trial teams, it is not made clear whether this synthesis was planned in advance of the start of both trials. The report merely notes that the US FDA and National Cancer Institute approved the joint analysis plan, which may reflect the expectation that neither trial alone would demonstrate a positive result. Comparisons are further hampered by the omission of crucial overall and disease-free survival data, as well as information on cardiotoxicity. However, it is clear that Herceptin can precipitate severe heart failure in some patients. The best that can be said about Herceptin's efficacy and safety for the treatment of early breast cancer is that the available evidence is insufficient to make reliable judgments. It is profoundly misleading to suggest, even rhetorically, that the published data may be indicative of a cure for breast cancer.

Drug regulatory agencies and bodies such as NICE play an important part in translating research evidence into clinical guidance. It is vital that their decisions are made carefully after considering the totality of available evidence. They must be free from political, special interest, or media influence, no matter how well meaning. The debate about the availability of Herceptin to women with early breast cancer demands cooler heads than have so far prevailed, in politics, in public, and even in medical journals. ■ *The Lancet*