Demand cancer drugs that truly help patients

Drug regulators and trial designs should assess benefits that actually matter to people with cancer, says **Ajay Aggarwal**.

Already this year, the US Food and Drug Administration (FDA) has approved or extended the use of several cancer drugs that have yet to show they will prolong life or improve its quality. Unfortunately, there is no guarantee that such benefits will be demonstrated over time, and these drugs, like most cancer treatments, increase the risk of side effects such as diarrhoea and susceptibility to infection.

In my view, regulators should ensure that drugs benefit patients before allowing them to persist on the market.

As part of my work as an oncologist, patients sometimes show me headlines that describe new cancer drugs with words such as 'game changer' and 'breakthrough'. Like my patients, I'm excited to see what therapies are on the horizon. Unfortunately, these words are rarely the ones that come to mind when I appraise evidence from clinical trials. Many trials aimed at getting drugs to market depend on surrogate end points such as slowed tumour growth. However, a drug that shrinks tumours might not help to extend people's lives. This is why most oncology drugs enter the market without clear evidence that they improve either the quality or the length of life.

In 2017, my colleagues and I completed a study of all 48 cancer drugs approved by the European Medicines Agency between 2009 and 2013 (C. Davis *et al. Br. Med. J.* **359,** j4530; 2017). Of the 68 clinical indications for these drugs (reasons to use a particular drug on a patient), only 24 (35%) demonstrated evidence of a survival benefit at the time of approval. Even fewer provided evidence of an improved quality of life for symptoms such as pain, tiredness and loss of appetite (7 trials; 10%). Most indications (36 of 68) still lacked such evidence three or more years after approval. Other groups in other regions have observed similar trends. For example, a 2015 study demonstrated that only a small proportion of cancer drugs approved by the FDA improved survival or quality of life (C. Kim and V. Prasad *JAMA Intern. Med.* **175,** 1992–1994; 2015).

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Once the medicines appear on the market, companies and patient advocates argue that any delay in governments covering costs for these drugs will bring about pain, suffering and unnecessary deaths, even when benefits have not been demonstrated.

If a drug does offer benefits, clinical trials are usually the best setting for these to shine through. People with cancer who are enrolled in clinical trials tend to be younger and much fitter than the general patient population. Because side effects are often worse for older or less-fit patients, benefits might not be realized or noticed in typical care settings.

Clinical trials, drug regulation and the field of medicine are all complicated. Societal values vary by country; improved survival rates might be assessed differently for different cancers, depending on how long people diagnosed with cancer are expected to live. Studies show that people's expectations about a drug's ability to extend life often far exceed what is observed. Clinicians should have honest conversations with patients to learn what constitutes a meaningful benefit for each individual.

When we choose treatment options for advanced cancer (the main indication for new cancer-drug approvals), we must consider that toxicities related to treatments may shorten life expectancy rather than extend it, and we should ensure that treatments do not diminish quality of life. Unfortunately, many clinical studies either neglect quality-of-life measures entirely or rely on unvalidated instruments. One seminal study demonstrated that people with advanced lung cancer who had early access to palliative care alongside standard treatments had greater improvements in quality of life and survival, despite receiving fewer aggressive end-of-life treatments (J. S. Temel *et al. N. Engl. J. Med.* **363,** 733–742; 2010).

Regulators also need to focus on more measures that people value: reduced toxicity, and the ability to maintain enough function to return to work or keep up social ties.

Some argue that the time required for randomized, controlled trials with meaningful measures would take too long. However, there have been innovations in designing robust trials measuring overall survival and quality of life, even in slowly progressing diseases such as prostate cancer.

Approvals that let drugs stay in the marketplace on the basis only of quick, easy surrogate end-points are unlikely to produce highly effective treatments; we will simply get more drugs providing marginal value.

I believe that the low bar also undermines innovation and wastes money. Copycat drugs with minimal benefits will continue to be approved on the basis of surrogates, and so will minimize incentives for true breakthroughs and game changers. At the same time, a large influx of drugs bringing limited benefit will force governments to spend a greater proportion of health funding on cancer drugs rather than on other treatment options.

Another risk is that emerging, heavily marketed drugs could blind clinicians and patients from looking anew at existing options that might bring bigger benefits. It amazes me how much attention is given to drugs even as people with cancer struggle to access surgery and radiotherapy. Investment in screening and diagnostics research also falls far behind that of drug research.

Ultimately, I want to access the best available therapies for the people I treat: the ones most likely to bring meaningful improvements in their quality and length of life, and the ones that reduce the toxicity associated with treatment. Any new cancer therapy, drug or not, should undergo robust evaluation for outcomes that truly matter to individuals. As it is, limited finances are too often being directed from evidence-based therapies to those that promise false hope. ■

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