Patient need, drug development, and risk

On March 21, 2019, the US FDA suspended all clinical trials investigating the use of venetoclax—a BCL-2 inhibitor—for the treatment of patients with relapsed or refractory multiple myeloma. The decision was based on interim results of the phase 3 BELLINI trial, which showed an increased risk of death for patients who were treated with venetoclax and bortezomib compared with placebo (41 [21·1%] deaths in 194 patients in the venetoclax group *vs* 11 [11·3%] of 97 in the control group; hazard ratio 2·03 [95% CI 1·04–3·94]). The FDA's decision raises important questions with respect to the safety of new treatments, their justification in disease settings with existing approved drugs with similar efficacy, and a growing trend in the way innovative therapies are pushed through clinical trials at breakneck speed.

In the case of multiple myeloma, drug innovation is at an all-time high. In late 2018, at the American Society of Hematology annual conference, at least six presentations showed promising results with the use of CAR T-cell therapy, one of which—the phase 1/2 LEGEND-2 study—led to the European Medicines Agency granting a PRIority MEdicines designation to LCAR-B38M. These early decisions certainly encourage pharmaceutical innovation and facilitate patient access to new drugs, but they also reflect a worrying trend in which regulators are arguably approving drugs too soon on the basis of early-stage results or uncontrolled phase 2 data for which the efficacy or harm of the new intervention is still too unpredictable. Additionally, regulators should be more cautious when drugs skip early-phase testing and move straight to a phase 3 trial for diseases in which there are already proven therapies. In the case of the BELLINI trial, researchers justified the investigation of venetoclax for multiple myeloma treatment based on encouraging results of the drug in chronic lymphocytic leukaemia and acute myeloid leukaemia, each of which led to breakthrough designations by the FDA. But decisions such as these show that different diseases will ultimately respond differently to treatment, even if they show similar disease characteristics or are based on similar trial populations. Being aware of the ultimate risks and benefits involved is a necessary first step to ensure clinical trials are being done to generate the best possible evidence needed, not to see whether the drug is effective in as many malignancies as possible to maximise commercial opportunity.

If the risks involved in enrolling patients in experimental clinical trials were apportioned the correct amount of caution, then unwarranted harms such as those seen in the BELLINI trial might be avoided. Indeed, in a recent study in *JAMA Internal Medicine*, researchers found that doctors' conversations with families about care for critically ill patients failed to take the time to explain the benefits and harms of treatment options and failed to address patients' values and preferences. When patient preference is so central a concern to deliver optimal cancer care, it is crucial that those responsible for the advent of new trials—such as funders, ethics approval committees, regulators, doctors, and investigators themselves—accurately communicate the dangers involved so that overtly risky or futile trials are avoided, whilst still encouraging various treatment avenues that are available to the patient.

Somehow, the unbridled promotion of new treatments driven by industry-sponsored research, research pressures, and treatment enthusiasm, has fostered a culture in which the promise of miraculous cures overshadows more important questions surrounding the realities of the risks and harms of treatment, the evidence base used to promote their use, and the actual need for new treatment options to be available in any given setting. Although it is important that some types of research are incentivised by accelerated approval mechanisms, this does not mean the threshold for safe and reliable evidence should be any lower. Moreover, both regulators and clinicians have a duty of care to ensure risks are communicated as fully and as transparently as possible, and thus ensure that patient care, best practice, and best evidence ultimately comes first.

■ *The Lancet Oncology*

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For more on the **FDA's decision on the BELLINI trial** see https://www.fda.gov/Drugs/DrugSafety/ucm634120.htm

For the **study on care for critically ill patients** see https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2729390