Trials and tribulations

Growing public interest in earlier access to experimental drugs for life-threatening conditions such as cancer has stimulated proposals for legislation that would promote or even create rights to access. But if the importance of properly conducted clinical trials is not valued appropriately, such actions could be detrimental to drug development and patient care.

In January this year, a study was published suggesting that a potential anticancer drug could inhibit tumour growth in rats[1]. But compared with many such studies published each year, this one has had a far larger impact. Why? At first glance, the paper might lead a reader to infer that this could be due to the promising results or the novelty of the compound's proposed mechanism of action: targeting differences in the mitochondria of cancer cells compared with normal cells. However, other factors have been much more important.

Most notably, press coverage of the study created considerable interest in the compound — dichloroacetic acid (DCA) — as an anticancer agent with potent activity without apparent toxicity. But in contrast to most investigational anticancer drugs, DCA is both non-patentable and commercially available. Coupling these factors with the relatively safe profile of DCA in some human studies for mitochondrial diseases has fuelled the initial interest in DCA to such an extent that there are now web sites dedicated to selling the compound, as well as providing information aimed at helping people to use it and to report their progress.

Although the aim of such initiatives is to help patients in desperate need of effective treatments, on the basis of historical success rates of anticancer drugs, it seems probable that at best the situation of most patients taking DCA might not be worsened. Recent estimates suggest that ~95% of cancer drugs that enter clinical development fail at some point, primarily due to ineffectiveness or unacceptable toxicity[2]. Given the complexity of cancer, there is no compelling reason to believe that DCA is significantly more likely to be an effective treatment than previous potential anticancer agents that showed promise in preclinical tests. Furthermore, as with any potential drug, lack of toxicity is not guaranteed, particularly bearing in mind that DCA is not necessarily being sourced from manufacturers aiming to make pharmaceutical-grade material.

Potentially far more damaging to the goal of helping cancer patients in general, however, is the impact that this initiative could have on the development of DCA as an anticancer drug. Efforts that are underway to conduct properly controlled trials with the compound could be jeopardized completely by anecdotal reports of side effects from DCA users. Furthermore, if it is possible for any patient to obtain DCA for treatment, the incentive to enrol in a clinical trial testing it is dramatically reduced.

The issues raised by the unusual developments with DCA provide a timely illustration of the potential pitfalls of some recent efforts to expand access to investigational drugs. Further facilitating compassionate access could be appropriate, but some proposals have broader demands. Last year, in an ongoing case between the FDA and the Abigail Alliance, a patient advocacy group, the US Court of Appeals for the District of Columbia controversially ruled that patients with life-threatening diseases have a constitutional right to access unapproved drugs. Furthermore, a bill known as ACCESS (S.1956) introduced to the US Congress, which is supported by the Abigail Alliance, proposes that a form of drug approval could be granted on the basis of highly preliminary evidence of safety and effectiveness from Phase I trials.

Even putting aside other thorny issues such as reimbursement, drug availability and potential liability, given the small number of patients in Phase I trials and historical failure rates for potential anticancer drugs (~90% for those that are successful in Phase I trials[2]), it seems that, as with DCA, the most probable outcome of a patient receiving such a drug would be that it is ineffective, and it could worsen their condition. And again, if such access outside clinical trials becomes widespread, how much incentive to enrol in a trial would remain?

Indeed, there is already a shortage of patients willing to participate in trials of anticancer agents, which could become more acute now that investment in cancer research is increasingly being translated into innovative potential drugs; cancer is already surpassing all other therapeutic areas in terms of the number of trials being conducted. With such promise in the pipeline, concentrating resources and effort on accelerating trials (for example, by enhancing patient recruitment and using adaptive trial designs) could be much more likely to improve outcomes for cancer patients than inappropriately widening access to highly unproven treatments and risking throwing drug development into complete disarray.

1. Bonnet, S. *et al. Cancer Cell* **11**, 37–51 (2007).
2. Kola, I & Landis, J. *Nature Rev. Drug Discov.* **3**, 711–716 (2004).