Accelerating drug development

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All human clinical trials of new treatments begin with phase I, where drugs are tested in isolation to confirm their safety. Yet most effective cancer treatments use a combination of drugs, so-called 'multi-agent' treatments. After phase I trials are completed, it can sometimes take up to two years before multi-agent trials are approved, never mind conducting the lengthy phase II and III trials necessary before a new drug finally reaches the market.

Professor Adrian Harris at the University of Oxford is currently leading

a new type of trial which aims to significantly accelerate multi-agent drug development. Working with the Cancer Research UK Drug Development Office (DDO) and AstraZeneca, Professor Harris' team are now running phase I trials of a new cancer drug, AZD0424.

The big difference with this trial is that researchers and patients will not need to spend years waiting for approval after phase I is complete. Since the trial was awarded flexible approval right from the start, researchers will be able to move straight to multi-agent trials to begin testing the new drug in three different 'arms'. Each treatment arm will pair AZD0424 with a pre-approved cancer drug from a shortlist of 5.

All drugs on the shortlist have been approved for use in the trial, and the final three partner drugs will be chosen based on experiments in mice currently being undertaken at the Edinburgh and Belfast Cancer Research UK Centres. Refining the choice of partner drugs while phase I trials are underway in Oxford adds a further time saving to the development process, and is possible thanks to the advanced approval process.

'Although the drug may be effective on its own, we expect substantial synergy in combinations,' says Professor Harris. 'So the strength of this trial is that we are able to pair it with other drugs without having to wait for further approval between stages.'

AZD0424 works by partially blocking two proteins, Src and ABL1, which are abundant in cancerous tissue. These proteins are important for cell growth, metastasis (the spread of cancer) and blood vessel development, so blocking them helps to halt the growth of cancer cells and shuts off their blood supply. Researchers have selected a list of drugs whose effects are expected to complement AZD0424, and the results from Edinburgh and Belfast will help decide which ones to use.

'By pairing this drug with others, we can block multiple signalling pathways to improve the overall treatment,' explains Professor Harris. 'We hope that they will have additive or synergistic effects which could reduce or inhibit tumour growth.'

When the overall effect of multiple drugs is equal to adding up their individual effects, this is known as additive. Synergistic effects are when drugs interact such that the result is greater than the sum of their individual effects. The partner drugs have already been shown to work individually, but this trial is about finding their combined effects in humans.

'With conventional trial structures, it's unlikely that we would be investigating this drug in a multi-agent trial,' says Professor Harris. 'The flexibility to adapt the treatments used in the multi-agent stage will allow us to match specific patient groups and cancer types to the most promising drug pairs for their circumstances. By removing the considerable cost and delay of waiting for approval between stages, we can widen the pool of viable treatments and accelerate drug development .'

Yet doesn't removing this stage compromise the safety of the trials? Not according to Professor Harris. 'The approval granted before phase I was no less rigorous than it would have been if it was given between phases,' he explains. 'All of the drugs used in the trial have been tested for safety. One of the reasons for choosing AZD0424is that similar drugs have minimal side effects, so it's a relatively low-risk compound to begin with. We will also reduce the dosage when we begin the multi-agent phase.'

Of course, this multi-arm trial design isn't suitable for all drugs. It does take a little longer to get advanced approval in the first place, delaying the start of phase I. The design is well suited to a drug like AZD0424,

which is expected to be most effective when used with other drugs. It is also important that patients in the trial receive good clinical care at all times.

'Professor Mark Middleton leads the clinical side,' says Professor Harris. 'He's currently running the phase I clinic, and every day he provides the highest quality of care to all patients in the trial. It's important that patients are treated holistically in the clinic.'

If the trial proves successful, Professor Harris hopes that the drug could be licensed for use with partner drugs within 4-5 years. 'It's worth remembering that by using combined approaches, including radiotherapy and surgery, half of common cancers are now curable,' he adds. 'A lot of people don't realise how far we've come in recent years. While there is still much work to be done, existing treatments for many cancers are highly effective. People often forget that, and it's important to focus on the positive sometimes.'

More information: Details of the trial at Cancer Research UK: www.cancerresearchuk.org/cance … vanced-solid-tumours

Provided by Oxford University