One mouse at a time: new approach to testing potential drugs for children's cancers

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A team of researchers in the US and Australia have developed a way of testing potential drugs for children's cancers so as to take account of the wide genetic diversity of these diseases.

In new research to be presented at the 32th EORTC-NCI-AACR Symposium on Molecular Targets and Cancer Therapeutics, which is taking place online, Professor Peter Houghton, director of the Greehey Children's Cancer Research Institute (San Antonio, U.S.), said that instead of conventional testing designs, which use multiple mice as models for rare children's cancers, analysis had revealed that it was possible to evaluate them on a single mouse.

Conventional testing is able to test only a few cancers at a time; however, these new findings mean that single mouse testing can be used to evaluate the action of more anti-cancer drugs against more tumours and more genetic variants of the same cancer in order to represent the clinical diseases more accurately. This could help to accelerate the development of better treatments for children's cancers.

Prof Houghton said: "Over the past decade, genetic studies have shown that cancers in children that were once considered homogenous in nature are in reality quite heterogenous, and may represent different 'diseases' that would respond differently to treatments. More importantly, such differences may be exploited therapeutically. Conventional drug testing in mice can identify active drugs but is restricted by the number of cancer mouse models that can be used due to resource constraints."

New drugs, or re-purposing of existing drugs, have to be tested in animal models of diseases before being evaluated in humans. This involves taking a sample of a particular tumour and grafting it into mice that have had their immune systems disabled to see how it responds to the treatment, known as patient-derived xenografts. In this study, patient-derived xenografts from 90 acute lymphoblastic leukaemias and 50 solid tumours in children were used to evaluate small molecule drugs and antibody drug conjugates (ADCs) - drugs that combine monoclonal antibodies with anti-cancer agents and are designed to target and kill tumour cells while sparing healthy cells.

Prof Houghton's centre is part of a group of laboratories, each focused on particular childhood cancers, that are part of the Pediatric Preclinical Testing Consortium (PPTC), funded by the US National Cancer Institute (NCI) to test new anti-cancer drugs.

He said: "One of the limitations of this testing programme is that when using conventional testing, which involves ten mice per treatment group, only a limited number of tumour models can be used and these do not necessarily reflect the genetic or epigenetic diversity of the clinical disease. We retrospectively analysed data from the PPTP and asked a simple question, 'would we have obtained the same results if we had used one mouse per treatment rather than ten mice?'.

"The results for response were similar to conventional testing. Our analysis of more than 2,100 drug/tumour model studies showed that 78% of single mouse tests correctly recapitulated the average response from testing according to the conventional experiment design with around 95% agreement. Basically, we could have generated exactly the same data using one mouse instead of ten."

In the study presented to the Symposium, the researchers prospectively investigated conventional testing and single mouse testing for three drugs

in acute lymphoblastic leukaemias (topotecan, birinapant and eltanexor), and for two ADCs in solid tumours (trastuzumab-deruxtecan and mCD276-PBD).

"In the single mouse testing, each mouse carries a different patient-derived tumour xenograft: you can think of each mouse as an individual 'patient'," said Prof Houghton. "For leukaemias, Richard Lock's group at the Children's Cancer Institute in Australia, a consortium member, used 80 to 90 different patient-derived leukaemia xenograft models and for solid tumours between 31 to 34 models. While the conventional approach gave us statistically significant results in the few models tested, the single mouse testing allowed for identification of subgroups of tumours that have exceptional response to particular drugs.

"Results from conventional testing and single mouse testing were essentially identical in 47 studies where both approaches used the same tumour model. In the leukaemia study we used 90 mice, whereas to attain the same information using conventional testing would have required 1,800 mice. For the solid tumours, it was 34 mice as opposed to 680 mice.

"In practical terms this means we could save resources and use fewer animals. However, of greater importance is that, with the same allocation of resources, we could increase the number of animal tumour models within a particular type of cancer by up to 20-fold to see how the drugs performed in different genetic or epigenetic variants of that disease.

"Single mouse testing may be particularly valuable for identifying responsive tumour types and biological markers that are associated with tumour response, including which different cancer therapies different tumour types may respond to. This could speed up the development of new and better therapies for childhood cancers. For example, for trastuzumab-deruxtecan, reported here, five of the most responsive

models are extracranial rhabdoid tumours of infants."

He concluded: "The study also contributes to the shift in how we undertake preclinical testing, and will facilitate testing of molecularly targeted agents relevant to paediatric cancer, as mandated by the Research to Accelerate Cures and Equity for Children Act (RACE for Children Act). This act requires the US Food and Drug Administration to develop a list of molecular targets and molecular targets of new drugs and biologics in development. If agents are determined to be substantially relevant to the growth and progression of paediatric cancer, this may trigger the requirement to investigate them further in children. This will require approaches to preclinical testing that incorporate models accurately representing the genetic and epigenetic heterogeneity of children's cancers. Single mouse testing addresses this issue and the NCI has now embraced the approach."

Professor Emiliano Calvo is co-chair of the EORTC-NCI-AACR Symposium on behalf of the EORTC; he is Director of START Madrid Group in Madrid, Spain, and Director of Clinical Research at the START Madrid-Centro Integral Oncológico Clara Campal hospital in Madrid and he was not involved in the research. He commented: "These findings suggest that single mouse testing is a valid way to identify anti-cancer drugs that may show activity in a broad range of tumours or only in a small sub-set of tumours. This approach is particularly important for children's cancers. As childhood cancer is a rare but diverse set of diseases, it can take longer for the research community to identify drugs or new biological targets against which anti-cancer therapies can be aimed. Anything that can speed up the testing of treatments is to be welcomed and this study raises awareness in the research community that single mouse testing is not only accurate but also provides us with far greater power to identify genetic biomarkers associated with tumour response."

More information: Abstract no: 37, "Prospective Validation of Single Mouse Testing (SMT) by the Pediatric Preclinical Testing Consortium (PPTC)", by Peter Houghton et al, presented in the Poster Discussion session 'Cancer therapeutics: preclinical modeling and patient stratification', 22.00-23.10 hrs Saturday 24 October, channel 2: cm.eortc.org/cmPortal/Searchab … ctdetails/0000898590

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