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Simple test could improve treatment for biggest leukaemia killer

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A simple blood test capable of detecting trace levels of leukaemia cells remaining after intensive chemotherapy has been developed by scientists at the National Institute for Health Research (NIHR) Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London.

The test can predict which patients with acute myeloid leukaemia (AML) are at risk of their cancer returning in the future, helping to guide doctors on what further treatment is needed.

A similar test revolutionised treatment for the most common form of childhood leukaemia when it was introduced nearly a decade ago. It is used to separate children into high and low intensity treatment groups depending on how they respond to the first stages of chemotherapy. This is the first time that this type of test has been used for the most common adult form of acute leukaemia.

In research published online in the *New England Journal of Medicine*, scientists used a 'minimal residual disease' (MRD) test to predict relapse, using blood samples from 346 AML patients who had undergone two cycles of chemotherapy. The patients all had AML driven by faults in the NPM1 gene, which the new test can identify. NPM1 mutated AML is the most common genetic sub-type of the disease and accounts for a third of all cases.

AML is a type of blood cancer diagnosed in around 2,400 people each

year in the UK and survival rates are extremely poor, with fewer than two in 10 patients surviving for more than five years. The leukaemia can be cured in patients who are able to tolerate intensive treatment and outlook is better in these patients.

The best chance of a cure involves intensive chemotherapy, but it is very common for AML to come back or 'relapse'. When doctors think that a patient is at high risk of their leukaemia returning, they can often be treated with a stem cell transplant. Finding a donor can take time and the treatment itself is very hard for patients, so knowing exactly who is likely to need a transplant is important.

The researchers found that MRD testing was far superior at predicting relapse compared to current methods, which mainly rely on analysis of genetic abnormalities within individual patients' cancer cells that influence whether they are 'high risk' or 'low risk' at the start of treatment.

The MRD test can determine if a patient is in 'molecular remission', which means there are no signs of the faulty genes indicative of leukaemia cells in their blood. In 82% of cases in which the MRD test detected the presence of the NPM1 cancer gene in a blood sample taken after initial treatment, the patient had relapsed within three years. Just 30% of patients who had no detectable leukaemia cells in their blood at this stage went on to relapse within that time.

Molecular relapse occurs long before any physical or clinical signs of relapse are apparent. The MRD test could help doctors to monitor patients after treatment and take pre-emptive action before full-scale relapse occurs. This can be measured to a sensitivity of one leukaemia cell in 100,000 healthy blood cells. Sequential testing over time can identify nearly all patients who will relapse before any clinical signs appear.

The research was funded by the blood cancer charity Bloodwise and the National Institute for Health Research (NIHR) and embedded in the Cancer Research UK-funded National Cancer Research Institute (NCRI) AML17 trial, sponsored and run by from Cardiff University under Chief Investigators Professor Alan Burnett and Professor Nigel Russell, Nottingham University Hospital. The trial treated patients from across the UK, Denmark and New Zealand. All samples analysed using MRD testing were from patients determined to be at 'standard risk' of relapse using existing testing.

Professor David Grimwade, Principal Investigator at the NIHR BRC at Guy's and St Thomas' and King's College London who led the research, said: "Conventional methods for guiding treatment for this aggressive type of leukaemia are inadequate. The MRD test is an invaluable tool to assess treatment response and identify those patients for whom chemotherapy is not sufficient and require stem cell transplantation or new treatments."

Alasdair Rankin, Director of Research at Bloodwise, said: "Research to improve the treatment for acute myeloid leukaemia is really important as current treatment is very demanding and survival rates are not good enough. Identifying people who can benefit from a stem cell transplant accurately and as early as possible would give them the best chance of success and could also protect some people who don't need a transplant from unnecessary treatment."

Life Sciences Minister George Freeman MP said: "This ground-breaking study has the potential to have a major impact on the treatment for patients suffering this devastating condition. It is studies such as this which highlight the importance of the government's commitment to health research and collaboration with research charities. These exciting developments are being made possible thanks to our investment of more than £1 billion a year through the National Institute for Health

Research."

Dr Robert Hills, who coordinated the clinical trial and collected data for the project from the Haematology Clinical Trials Unit, based in Cardiff, said: "The data we've collected from patients has given us a new insight into Acute Myeloid Leukaemia (AML). Looking at the disease while people are receiving treatment has given us a unique opportunity to learn much more about how best to treat. What we have been able to identify is a group of patients who otherwise would be thought to do quite well, who in fact have a very poor prognosis, and who are not well served currently. This opens up the exciting prospect that we can do the same for other groups of patient as well."

More information: Adam Ivey et al. Assessment of Minimal Residual Disease in Standard-Risk AML, *New England Journal of Medicine* (2016). DOI: 10.1056/NEJMoa1507471

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