Missing DNA fragments hold clue to predicting childhood leukaemia relapse

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Australian researchers have developed a new risk scoring system for children with leukaemia based on missing DNA fragments or 'microdeletions'. The risk score will allow doctors to better predict the chance of relapse of a subgroup of kids currently hidden in a lower risk group. The finding was published today in the *British Journal of Haematology*.

The international study, led by Australian researchers at Children's Cancer Institute, discovered that searching for specific gene microdeletions found only in leukaemia, when combined with two other test results, provides doctors with a more accurate way to categorise patient risk than the current approach.

The study tested 475 patients from 6 different children's hospitals in Australia and New Zealand enrolled on a clinical trial sponsored by ANZCHOG, the Australian and New Zealand Children's Haematology and Oncology Group.

The patients were all children with non-high-risk B-cell precursor acute lymphoblastic leukaemia (BCP-ALL), a subtype of acute lymphoblastic leukaemia (ALL), the most common childhood cancer with survival rates typically near 90%. Most children with ALL have B-cell precursor acute lymphoblastic leukaemia.

Study leader, Associate Professor Rosemary Sutton, said the most intensive treatment for BCP-ALL patients was usually given to the 11%

or so of children in the high-risk category to limit side effects for kids who don't need it.

"Children in the standard and medium risk category in the study were given less intensive treatment than high-risk patients. But about one in six of them relapsed. Obviously, some children needed more intensive treatment than previously thought - but which ones?" she said.

A/Prof Sutton said she and her collaborators developed a new kind of risk score which builds on a bone marrow test, the minimal residual disease or MRD test developed at Children's Cancer Institute, which gives doctors early warning that treatment may not be working.

The MRD test is so sensitive it can detect just one cancer cell in a million bone marrow cells surviving cancer treatment. The test was a huge boon for some children with leukaemia on this same trial, since it alerted doctors that they had a very high risk of relapsing. Consequently, they were treated very intensively with chemotherapy and bone marrow transplants, and the survival rate of this subgroup doubled. But MRD alone is not enough.

"For the standard to medium risk group, we needed more information to get a better handle on the biology of the child's cancer to better determine their risk", said A/Prof Sutton.

"So, we supplemented MRD results with two other pieces of patient information, the presence or absence of specific gene microdeletions and a score called the NCI (National Cancer Institute) risk, based on age and white blood cell count.

"We tested for microdeletions in 9 genes involved in leukaemia and found that two of the genes, IKZF1 (called 'Ikaros') and P2RY8-CRLF2, were important predictors of relapse," she said.

These measures were combined to calculate a risk score for each patient of '0' (no risk factors), to '2+' (several). The study found that children with a '2+' score were most likely to relapse or die within 7 years after treatment started, while those with a '0' score least likely.

The same microdeletions were found to be important for predicting relapse in a cohort of Dutch children with leukaemia and the new scoring system was validated by researchers in The Netherlands.

If the new risk score system is adopted in future, doctors could give children with a '2+' risk more intensive treatment with the aim of improving their survival.

Dr Toby Trahair, paper co-author and oncologist at Kids' Cancer Centre at Sydney Children's Hospital, Randwick said the scoring system could make a big difference to the success of childhood leukaemia treatment.

"We are always trying to improve how we diagnose and treat children with this most common childhood cancer. This risk score will mean doctors can fine tune a child's risk category and so fine tune their treatment.

"It will mean more kids can conquer this horrible disease, which only 50 years ago had survival rates of close to zero" he said.

More information: Rosemary Sutton et al, A risk score including microdeletions improves relapse prediction for standard and medium risk precursor B-cell acute lymphoblastic leukaemia in children, *British Journal of Haematology* (2017). DOI: 10.1111/bjh.15056

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