New personalized therapy improves survival for patients with CLL leukemia, phase 3 trial finds

December 11 2023

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Personalized treatment for the most common form of adult leukemia helps patients survive for longer and stay in remission, a phase 3 trial has

found.

The trial, by the University of Leeds, is published in the *New England Journal of Medicine* and has been presented at the 65th American Society of Hematology (ASH) Annual Meeting and Exposition in San Diego. The journal paper is titled, "Chronic lymphocytic leukemia therapy guided by measurable residual disease."

The data shows that the duration of therapy can be individualized for each patient by using regular blood tests to monitor their response. In the trial, this approach resulted in significant improvements in both progression-free and overall survival in patients with previously untreated chronic lymphocytic leukemia (CLL). The effect was stronger among patients with poorer outcomes to standard treatments, such as those with some genetic mutations.

Adult patients were given a combination of cancer growth-blocking drugs over varied durations depending on how rapidly their disease responded.

The trial found that this approach significantly improved progression-free and overall survival compared to the standard treatment for CLL, with more than 19 in 20 patients in remission three years after starting treatment.

The study, named FLAIR, is a phase 3 randomized controlled trial for untreated CLL, taking place in more than 100 hospitals across the UK.

Lead author Peter Hillmen, Professor of Experimental Hematology in the University of Leeds' School of Medicine, and Honorary Consultant Hematologist at Leeds Teaching Hospitals NHS Trust, said, "Our findings show that, for this group of patients, the treatment is very effective at tackling their disease and is well tolerated by them."

"This means that patients on our trial had better outcomes while also enjoying a better quality of life during their treatment. Most patients treated with the new combination have no detectable leukemia in their blood or bone marrow by the end of treatment which is better than with previous treatments and is very encouraging."

Dr. Iain Foulkes, Executive Director of Research and Innovation at Cancer Research UK, said, "We are delighted to see these results from the FLAIR trial which show the importance and effectiveness of tailoring cancer treatment to the individual patient. Not only this, but the trial has found a way to do so without requiring frequent bone marrow tests which are more invasive and can be painful."

"The collaborative effort that went into this trial—involving researchers, health care professionals, funders and dedicated patients and their families—point to a new standard of care which could see real progress made against leukemia."

Chronic lymphocytic leukemia is a type of cancer that affects the blood and bone marrow. It cannot usually be cured but can be managed with treatment. More than nine in 10 people are aged 55 and over when they are diagnosed.

Current treatments include chemotherapy, immunotherapy, or cancer growth blockers.

The FLAIR trial tested cancer growth blockers called Ibrutinib and Venetoclax (I+V). Also known by the brand names Imbruvica and Venclexta, these are usually administered either continuously or for the same fixed duration rather than tailored to each patient's response. This means that many patients may stop treatment too early and don't get the full potential benefit from their therapy or continue therapy for longer than necessary. This could lead to a greater chance of relapse of their

leukemia and/or of treatment side effects.

FLAIR researchers aimed to discover whether it was possible to personalize I+V treatment duration for patients based on regular blood sampling and/or bone marrows, and whether this was as effective or better than standard treatment (FCR).

This regular blood and bone marrow monitoring gave researchers a more up-to-date picture of how patients were responding to I+V, and meant that the duration of I+V treatment could be tailored accordingly to each patient. In addition, it was found that basing the duration of treatment on less invasive, quicker blood samples was just as effective as using bone marrows, which can be painful and sometimes require sedation.

FLAIR was launched in 2014, recruiting 1,509 patients with CLL. They were randomized to four treatment groups, each receiving a different treatment.

This part of the FLAIR trial compared two of the groups, placing 260 patients on I+V and 263 on the standard treatment, known as FCR. Almost three-quarters were male, which was to be expected as CLL occurs more frequently in males. The average age was 62, and just over a third had advanced disease.

At the end of this stage of the trial, 87 patients had seen their disease progress, 75 of which were on FCR, and 12 on I+V.

To date, 34 of these patients have died during the trial. Of these, 25 were treated with FCR and only nine with I+V.

The patients on I+V underwent blood tests and bone marrows to monitor their response to treatment. The technique used is known as measurable residual disease (MRD) which allows clinicians to see the number of

remaining cancer cells. The number of cells may be so small that the patient is asymptomatic. An MRD positive test result means that there are remaining cancer cells.

The research team now hopes that this more personalized therapy approach, guided by blood test monitoring will be adopted as a new standard of care for patients needing first-line CLL treatment.

Professor Hillmen said, "The results of the FLAIR Trial, led by the Leeds Cancer Research UK Clinical Trials Unit at the University of Leeds, are exceptional and herald a change in the way chronic lymphocytic leukemia will be treated. FLAIR has been a huge collaborative effort over the last decade by the UK's leading CLL specialists and by the hematology teams in over 100 hospitals throughout the UK. The participation of patient groups, individual patients and their families were critical to delivering such progress particularly through the challenges of the pandemic."

The trial was coordinated by the Leeds Cancer Research UK Clinical Trials Unit at the University of Leeds. Deputy Director Professor David Cairns said, "The vision of the Leeds Cancer Research UK CTU is to improve the length and quality of survival for cancer patients on a worldwide scale. Our strategy to do this is to ensure that we build evidence to identify the correct treatment, for the correct duration, for the correct patient."

"FLAIR is a trial well aligned to our strategy, and reflects team science including clinicians, laboratory scientists, methodologists and operational experts working together to deliver important trial results. None of this would be achieved without the selfless commitment of trial participants who contribute their time and data."

More information: Talha Munir et al, Chronic Lymphocytic

Leukemia Therapy Guided by Measurable Residual Disease, *New England Journal of Medicine* (2023). DOI: 10.1056/NEJMoa2310063