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Study shows combining chemotherapy with targeted drug boosts response in chronic lymphocytic leukemia

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Among younger patients newly diagnosed with chronic lymphocytic leukemia (CLL), treatment with a combination of chemotherapy and a molecularly targeted drug significantly improves response over what is typically seen with chemotherapy alone, according to an investigator-initiated multi-center phase II clinical trial.

"We're combining the most potent chemotherapy regimen with a highly active novel agent, trying to develop an optimal regimen for younger patients," said Matthew Davids, MD, MMSc, Associate Director, Center for Chronic Lymphocytic Leukemia, Dana-Farber Cancer Institute, who reported on the study in an oral presentation at the 59th American Society of Hematology (ASH) Annual Meeting and Exposition in Atlanta.

Patients in the trial, who were physically fit and 65 years of age or younger, first received up to six months of a combination of the targeted oral agent ibrutinib and FCR (fludarabine, cyclophosphamide, and rituximab) chemotherapy. This therapy combination has been a standard treatment for younger and physically fit patients with CLL. The patients then were given ongoing maintenance with ibrutinib.

All of the 35 people who received this "iFCR" combination responded to the treatment. At the conclusion of the chemotherapy portion of the treatment, 37% had achieved complete response with no detectable signs

of minimal residual disease (MRD) in the bone marrow, compared to the 20% rate seen historically with FCR alone.

"More strikingly, over time these responses deepened in a substantial number of patients who continued on ibrutinib monotherapy as a maintenance strategy," Davids said.

During the post-FCR ibrutinib maintenance period, the rate of MRD-negative complete response rose to 57%, with 83% showing MRD-negativity in the bone marrow. FCR is known to provide prolonged disease-free survival for many CLL patients with a mutated IGHV gene, but less durable responses for patients with unmutated IGHV. Even among trial participants with this higher-risk unmutated IGHV, 71% became MRD-negative in the bone marrow.

"As far as we know, that's the highest rate anyone has ever reported for this group with any regimen in CLL," Davids said.

While the average age of diagnosis in CLL is 72 years old, older patients often don't tolerate FCR chemotherapy very well. This trial excluded those over 65 years of age.

"With older, frailer patients, in the past few years we've been moving away from chemotherapy and toward novel targeted oral agents such as ibrutinib alone or in combination with other novel agents," he said.

Approved by the Food & Drug Administration for the treatment of newly diagnosed CLL in 2016, ibrutinib targets a protein called BTK (Bruton Tyrosine Kinase) that CLL cells need to survive.

"Previous studies have demonstrated that when we use this agent alone, it's very effective at controlling the disease but it doesn't eradicate it," Davids said. "A goal in our field now is to try to combine targeted agents

such as ibrutinib with other drugs."

Patients given iFCR treatment saw relatively low rates of infection and blood toxicities, which may have been due in part to mandatory preventive dosing with antimicrobial agents and growth factors that help to rebuild populations of white blood cells after chemotherapy. Other research has suggested that ibrutinib itself might also help CLL patients restore their immunity, although this theory requires further study, Davids said.

To date, the iFCR trial has been carried out at Dana-Farber, Massachusetts General Hospital Cancer Center, and Duke University Medical Center. The study is now being expanded with a goal of recruiting 50 more patients, with support from the Blood Cancer Research Partnership, a research consortium started with a grant from the Leukemia and Lymphoma Society that Davids co-directs. In this new cohort, patients will stop getting ibrutinib after two years of maintenance if they are MRD-negative in the bone marrow, Davids said. He hopes that a phase III clinical study will eventually be launched to compare the iFCR regimen to standard of care in younger CLL patients.

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