Drug in new class of targeted therapies shows early promise against blood-related cancers

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A Phase I clinical trial of SNS-032, one of the first in a new class of drugs that inhibit cyclin-dependent kinases, demonstrated the drug's safety and potential clinical action against advanced chronic lymphocytic leukemia (CLL). Cyclin-dependent kinases are enzymatic proteins that are integrally involved in cellular metabolism, renewal and signaling, and are thought to play key roles in the growth of cancers. The drug did not demonstrate any clinical effect against advanced multiple myeloma, although researchers hope it might still prove to have some benefit against this blood cancer as part of combination therapy. The paper is published online in the *Journal of Clinical Oncology*.

"No drugs that target this cancer mechanism are on the market today," says study author David S. Siegel, M.D., Ph.D., Co-Chief, Multiple Myeloma, John Theurer Cancer Center at Hackensack University Medical Center. "I am hopeful that larger studies will show that this targeted therapy is useful against a number of advanced B cell malignancies."

Chronic lymphocytic leukemia (CLL) and multiple myeloma are both considered B cell malignancies, as they attack these cells, also known as B lymphocytes. B lymphocytes are white blood cells that develop in the bone marrow and make antibodies that protect the immune system. Both types of blood cancer leave their victims susceptible to infections and other serious complications. While there are treatments for both cancers, there is no cure, and more effective treatments are needed.

"At the John Theurer Cancer Center we are committed to exploring new treatment options for rare cancers, such as multiple myeloma and CLL," said Andrew L. Pecora, M.D., F.A.C.P., C.P.E., Chairman and Executive Administrative Director, John Theurer Cancer Center. "We will continue to research new therapies to help our patients live longer and to find a cure for these diseases."

Dr. Siegel and colleagues tested the new medication on 37 patients, 19 with CLL and 18 with myeloma. Patients recruited to the study had advanced disease that was in relapse, and all had been through previous treatments with other medications (median number of prior treatments: four). All patients were given SNS-032, and all were aware of what they were taking.

To test both the drug's safety and the best potential dose, SNS-032 was given intravenously as a "loading" dose - an initially higher dose that is then reduced to a maintenance level - over five minutes. This was followed by a six-hour infusion given to all patients on a weekly basis for three consecutive weeks.

Although the primary purpose of the study was to test the maximum safe dose that could be given to patients, Dr. Siegel and colleagues also looked at whether the medication had an effect on disease processes. One patient with CLL had more than a 50 percent reduction in measurable disease, but no improvement in disease markers in the blood. Another CLL patient had stable disease for four courses of treatment. For multiple myeloma, two patients had stable disease with treatment and one had normalization of spleen size, which is an indication of a reduction in blood cancer activity.

Looking at blood test results for the patients, the researchers found anti-cancer activity. The drug appeared to inhibit cyclin-dependent kinases 7 and 9, two of the three enzymatic proteins targeted in this study. They

also caused apoptosis, or cell death, in cancer cells.

"Our study found that this drug is well tolerated and had some clinical effect, but it is important to note that this was a small, very early stage study," says Dr. Siegel. "Based on these findings, there is justification for additional research, which will show whether this drug has a place in the arsenal of treatments for hematologic malignancies."

Preclinical studies of SNS-032 demonstrated that the drug inhibited the growth of cancer cells, and induced apoptosis, in B cell malignancies.

"The results of the preclinical studies suggest that we might see more anti-tumor effects if the drug is given over a longer period, possibly eight hours or more," adds Dr. Siegel. "Because the patients in the study were at a late disease stage and heavily pretreated, we might also see more of a response in earlier-stage patients. Future studies could look at these issues, as well as the feasibility of using SNS-032 in combination with other therapies."

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