MedicalXpress

High-dose Vorinostat effective at treating relapsed lymphomas

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Patients whose aggressive lymphomas have relapsed or failed to respond to the current front-line chemotherapy regimen now have an effective second line of attack against their disease. Reporting the results of a first-of-its-kind phase 1 clinical trial to test the effectiveness of a new class of drugs to augment standard chemotherapy, a team led by Fred Hutchinson Cancer Research Center scientists found that giving patients high doses of Vorinostat (suberoylanilide hydroxamic acid) in combination with another round of commonly used second-line drugs resulted in a 70 percent response rate, including several patients whose lymphoma cells disappeared entirely.

According to Ajay Gopal, M.D., associate member of the Fred Hutch Clinical Research Division and corresponding author of the paper, published online in the *British Journal of Haematology*, the study results open the way to potentially solve the dilemma of how to effectively treat patients when modern cancer drugs fail after the first try. And, he said, it sets the stage for using a new class of drugs called histone-deacetylase inhibitors (HDAC), of which Vorinostat is one, to sensitize tumor cells to the cancer-killing effects of chemotherapy.

Patients treated in the trial had several types of lymphoma, however the best responses were seen in those who had Hodgkin and diffuse large B-cell lymphomas, two of the most aggressive types that typically require a stem cell transplant to cure if they are not cured after the first line of treatment. Knocking back the cancer raises the likelihood for a successful transplant.

"The better the response, the better the outcome will be when patients proceed to a stem cell transplant designed to cure them of their disease," said Elizabeth Budde, M.D., Ph.D., a research associate in the Fred Hutch Clinical Research Division and first author of the study.

The researchers noted that while the current front-line chemotherapy drugs are the most effective yet against lymphomas, patients who relapse after receiving them are less likely to achieve long-term, disease-free survival when current second-line or "salvage" therapies are applied. This is because the cancers develop resistance to the drugs or the tumor's biology changes in some way to reduce their effectiveness.

Lymphoma refers to a group of cancers that strike the lymphatic system, which is a key part of the immune system. Lymphomas are broadly classified as either Hodgkin or non-Hodgkin. Some lymphomas are highly curable; others require complex treatment.

Preclinical studies at Fred Hutch and other research centers have found Vorinostat to be effective when used along with the standard chemotherapy combo, which is known by the acronym (R)ICE for rituximab, ifosphamide, carboplatin and etoposide. Vorinostat works by blocking signals to tumor-suppressor genes, which allows those genes to induce tumor cell death.

Vorinostat is approved by the Food and Drug Administration to treat cutaneous T-cell lymphoma. The standard dose is 400 milligrams per day. It is manufactured by Merck & Co.

The phase 1 trial involved 27 patients at about a dozen sites that are members of the Puget Sound Oncology Consortium. Because the drugs can be taken orally, the patients could self-treat at home. A novel two-stage dose escalation schedule developed at Fred Hutch was used to speed the time it took to determine the maximum effective dose of

Vorinostat with the fewest side effects, which was 500 milligrams twice a day.

Some level of response was observed in 19 patients, including eight complete responses. The most common side effects were gastroenterological, which led researchers to recommend giving future patients preventive medicines while taking Vorinostat.

Because many of the patients were destined for an autologous hematopoietic stem cell transplant as the next treatment step, researchers also evaluated the ability to mobilize and collect the patients' peripheral blood stem cells after the drug therapy was administered. They were successful in 20 of 21 patients.

Budde said the next step is to conduct a phase 2 study of patients who have diffuse B-cell lymphoma because the drug regimen worked best in these patients and it is the most aggressive of lymphomas.

More information: "A phase 1 study of pulse high-dose Vorinostat (V) plus rituximab (R), ifosphamide, carboplatin and etoposide (ICE) in patients with relapsed lymphoma" *British Journal of Haematology*, 2013.

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