MedicalXpress

AML patients have high response rate with vorinostat added to treatment

December 13 2011

Adding a drug that activates genes to frontline combination therapy for acute myeloid leukemia resulted in an 85 percent remission rate after initial treatment, researchers at The University of Texas MD Anderson Cancer Center reported at the 53rd Annual Meeting of the American Society of Hematology.

Results of the Phase II clinical trial of 75 patients set the stage for a national Phase III clinical trial of the new combination compared to standard-of-care frontline combinations used at MD Anderson and elsewhere, said study leader Guillermo Garcia-Manero, M.D., professor in MD Anderson's Department of Leukemia.

Study patients received the drug vorinostat, known commercially as Zolinza, a histone deacetylase inhibitor, in addition to the chemotherapy drug cytarabine and idarubicin, an anthracycline antibiotic commonly used as chemotherapy.

"The overall response rates are encouraging, and most higher risk patients did very well," Garcia-Manero said. He will be the principal investigator of the Phase III trial, which will be conducted through the National Cancer Institute's Cooperative Oncology Groups.

Vorinostat activates suppressed genes by protecting acetyl chemical groups that adhere to histone proteins, which are connected to DNA like beads on a string. Acetylated histones make genes more accessible for transcription, so vorinostat presumably works by reactivating blocked

tumor-suppressing genes.

According to the NCI's Surveillance Epidemiology and End Results database, about 14,000 new cases of AML are diagnosed annually in the United States and the disease kills about 9,000 people each year. AML is characterized by swift proliferation of immature white blood cells in the blood and bone marrow that crowds out normal cells, leaving patients exposed to infection, severe anemia and bleeding.

High response for higher risk patients

Overall, 57 patients achieved complete remission, and another seven had complete remission with incomplete platelets (CRp), for an overall response rate of 85 percent. Median overall survival was 82 weeks and median event free survival was 47 weeks.

Overall response rate for 11 patients with the high-risk Flt-3 ITD mutation was 100 percent, with 10 achieving complete remissions and the other a CRp. Their median overall survival was 91 weeks and median event free survival was 66 weeks.

Of 29 patients who were diploid (a pair of each chromosome, double the usual number), 25 had complete remissions and two achieved CRp, for an overall response rate of 93 percent. Their median overall survivial was 105 weeks and event-free survival was 68 weeks.

Seventeen patients with -5/-7 cytogenetic alterations fared less well, with a 64 percent overall response rate and median overall survival of 34 weeks and median event free survival of 14 weeks.

Side effects

No cardiac toxicities and no excess toxicity related to vorinostat were observed. Common side effects were diarrhea (72 percent), nausea and vomiting (65 percent) and skin toxicities (38 percent).

Nineteen patients who achieved either CR or CRp had blood stem cell transplants. Median overall survival and event free survival had not been reached for those patients.

Garcia-Manero said levels of two proteins, NRF2 and CYBB, were associated with longer survival.

Phase III clinical trial

There will be three arms for the randomized, blinded Phase III clinical trial:

• Standard frontline therapy of seven days of cytarabine infusion and three days of the anthracycline antibiotic daunirubicin.

• MD Anderson standard frontline therapy of three days of idarubicin with high-dose continuous infusion of cytarabine for four days.

• Three days of idarubicin, four days of cytarabine plus vorinostat.

Provided by University of Texas M. D. Anderson Cancer Center

provided for information purposes only.