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Combination therapy with midostaurin improves survival of AML patients with FLT3 mutations, phase 1

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A targeted drug that is active against acute myeloid leukemia (AML) is particularly effective when teamed with chemotherapy in patients whose cancer cells harbor a key genetic mutation, researchers at Dana-Farber Cancer Institute and their colleagues will report at the American Society of Hematology's (ASH) annual meeting on Monday, Dec. 7.

The Phase I study focused on the potential of administering the drug midostaurin (PK412) with high doses of the chemotherapy drug cytarabine in AML patients whose disease has been driven into remission by cytarabine and another chemotherapy agent, daunorubicin. Midostaurin is a kinase inhibitor, blocking a key class of enzymes - kinases - that often spur cancer cell growth. It works by targeting the FLT3 cell receptor, which is overactive in the white blood cells of many AML patients as a result of genetic mutation.

On its own, midostaurin reduces the number of circulating leukemia cells in AML patients, but rarely produces complete remissions. Preclinical studies have shown that FLT3 inhibitors like midostaurin work synergistically with chemotherapy agents, reinforcing each other's effect against cancer.

In the new study, researchers led by Richard Stone, MD, of Dana-Farber treated 40 newly diagnosed AML patients under age 61 with daunorubicin and cytarabine to induce remission, followed by high-dose

cytarabine and oral midostaurin in twice-daily doses of either 100 mg or 50 mg. The higher dose level often produced nausea and vomiting, but patients at the lower dosage tolerated the therapy well.

Of the 40 patients who completed the therapy, 32 (or 80 percent of the group) had a complete response, in which circulating AML cells were reduced to undetectable levels. Complete responses occurred in 74 percent of the patients whose cells had normal FLT3, and in 92 percent of those with mutated FLT3 - significantly better than had been achieved with midostaurin alone. Eighty-five percent of the group with mutated FLT3 were alive one year after treatment, and 62 percent were alive two years after. These results were comparable to those of the normal FLT3 group (81 percent one-year survival, and 62 percent two-year survival).

Although the study involved a relatively small number of patients, "the results suggest that a combination of an FLT3 inhibitor and chemotherapy might be effective enough to reduce the need for donor stem cell transplantation in AML patients with mutated FLT3 who have entered first remission," Stone says. "These findings also support the value of ongoing phase 3 studies of the potential benefits of midostaurin during various phases of AML treatment."

Source: Dana-Farber Cancer Institute

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