Clinical Trials

Major finding: T-DM1 improves survival in patients with HER2-positive metastatic breast cancer.

Concept: T-DM1 combines the anti-HER2 antibody trastuzumab and DM1, a cytotoxic microtubule inhibitor.

Impact: This conjugate specifically targets HER2-expressing tumor cells, thus reducing toxicity.

AN ANTIBODY–DRUG CONJUGATE IS EFFECTIVE IN HER2-POSITIVE BREAST CANCER

HER2 amplification occurs in a subset of breast cancers and is associated with poor prognosis. Targeted therapies directed against HER2, including the monoclonal antibody trastuzumab and the tyrosine kinase inhibitor lapatinib, provide clinical benefit to patients with HER2-positive advanced breast cancer, particularly when administered with chemotherapeutic agents such as capecitabine or taxanes. An alternative treatment approach is to direct cytotoxic drug delivery to HER2-expressing tumor cells using trastuzumab emtansine (T-DM1), an antibody–drug conjugate consisting of trastuzumab and DM-1, an inhibitor of microtubule assembly; prior phase II trials have shown that T-DM1 has activity in HER2-positive disease. To further assess the efficacy and safety of T-DM1, Verma and colleagues conducted a randomized, open-label phase III trial comparing T-DM1 with the standard combination of lapatinib plus capecitabine in 991 patients with centrally confirmed HER2-positive locally advanced or metastatic breast cancer who had been previously treated with trastuzumab and a taxane. The primary endpoints were progression-free survival (PFS), overall survival (OS), and safety, and key secondary endpoints included objective response rate and time-to-symptom progression. T-DM1 treatment prolonged PFS (9.6 vs. 6.4 months) and enhanced OS (30.9 vs. 25.1 months) compared with lapatinib plus capecitabine. In addition, treatment with T-DM1 resulted in an increased objective response rate (43.6% vs. 30.8%) and a longer duration of response (12.6 vs. 6.5 months). T-DM1 was generally well tolerated, with a lower incidence of grade 3 or 4 adverse events compared with lapatinib plus capecitabine (40.8% vs. 57.0%); the most commonly reported side effects were manageable with dose modification and included thrombocytopenia and elevated serum aminotransferase levels. These findings support the use of T-DM1 as an effective and well-tolerated treatment for patients with metastatic HER2-positive breast cancer. ■

Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, et al. Trastuzumab emtansine for HER2-positive advanced breast cancer. N Engl J Med 2012 Oct 1 [Epub ahead of print].

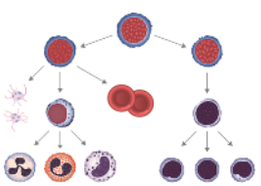
Leukemia

Major finding: A potent FLT3 inhibitor overcomes the differentiation block in patients with FLT3/ITD AML.

Approach: A clinical correlative study was performed using samples from patients enrolled in a phase II trial.

Impact: Kinase inhibitors can induce terminal differentiation of cancer cells.

QUIZARTINIB INDUCES TERMINAL DIFFERENTIATION IN AML BLASTS



Internal tandem duplication (ITD) mutations in *fms-related tyrosine kinase 3* (*FLT3*) occur in approximately 25% of patients with acute myeloid leukemia (AML) and are associated with a poor prognosis. Quizartinib is a potent inhibitor of the FLT3 receptor tyrosine kinase that is currently being evaluated in a phase II clinical trial for patients with FLT3/ITD AML. An interim analysis of this trial indicated that 71% of patients experienced a clinical response. Unexpectedly, although peripheral blasts were rapidly cleared, the patients' bone marrows remained hypercellular and bone marrow blasts continued to express FLT3/ITD. Sexauer and colleagues hypothesized that quizartinib induced AML blast differentiation and therefore evaluated bone marrow and blasts collected before and during quizartinib treatment from of a subset of patients enrolled in this trial. After several weeks of treatment, a significant increase in the mature myeloid cell population and a dramatic decrease in the number of blasts were observed in the peripheral blood and bone marrow of 13 of the 14 patients and were typically associated with a complete response. Moreover, the myeloid cells still expressed the FLT3/ITD, suggesting that these cells were directly derived from leukemic precursors. Interestingly, the 1 patient who did not respond and a second patient who ultimately experienced disease progression each had mutations in *CCAAT/enhancer binding protein α* (*C/EBPα*), which may represent a potential mechanism of resistance to FLT3 inhibitors. Indeed, in an *in vitro* system in which FLT3/ITD–expressing AML cells were cocultured with bone marrow stromal cells, *C/EBPα* knockdown significantly decreased quizartinib-induced differentiation of AML cells. These findings indicate that *FLT3* mutations block differentiation in AML and suggest that induction of terminal differentiation by kinase inhibitors may be an effective way to treat FLT3/ITD AML. ■

Sexauer A, Perl A, Yang X, Borowitz M, Gocke C, Rajkhowa T, et al. Terminal myeloid differentiation in vivo is induced by FLT3 inhibition in FLT3/ITD AML. Blood 2012 Sept 25 [Epub ahead of print].