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IN BRIEF

Midostaurin *(Rydapt)* for AML and Advanced Systemic Mastocytosis

The FDA has approved the oral multikinase inhibitor midostaurin (*Rydapt* – Novartis) for first-line treatment, in addition to standard chemotherapy, of adults with FLT3 (fms-like tyrosine kinase 3) mutation-positive acute myeloid leukemia (AML). About 30% of patients with AML have FLT3 mutations. Midostaurin is also approved as a single agent for treatment of adults with aggressive systemic mastocytosis, systemic mastocytosis with associated hematological neoplasm, or mast-cell leukemia. In mastocytosis, midostaurin targets mutant c-KIT, not FLT3.

In a randomized, double-blind trial, 717 adults 18-59 years old with newly diagnosed FLT3-mutated AML were treated with midostaurin (50 mg twice daily on days 8-21 of each 28-day cycle) or placebo in addition to standard chemotherapy (induction therapy with cytarabine and daunorubicin and consolidation therapy with high-dose cytarabine), followed by up to 12 additional maintenance cycles of midostaurin or placebo. More than half of the patients (57%) stopped treatment and underwent hematopoietic stem-cell transplantation during the trial. Median event-free survival was 8.2 months with midostaurin compared to 3.0 months with placebo, a significant difference. Median overall survival after a median follow-up of 59 months was significantly longer with midostaurin than with placebo (hazard ratio 0.78). The 4-year overall survival rate was 51.4% with midostaurin and 44.3% with placebo.[1] Common adverse effects reported in the midostaurin plus chemotherapy group at a rate at least 2% higher than in the placebo plus chemotherapy arm included febrile neutropenia (83% vs 81%), nausea (83% vs 70%), vomiting (61% vs 53%), and mucositis (66% vs 62%). There were no differences between the two groups in the rates of severe (≥grade 3) adverse events.

A single-arm, phase 2 study of midostaurin (100 mg twice daily in 4-week continuous cycles) included 89 adults with advanced systemic mastocytosis (16 had mast-cell leukemia) and evidence of organ damage. The overall response rate was 60%, and 45% of patients had a major response (complete resolution of at least one type of mastocytosis-related organ damage). The median duration of response was 24.1 months. Treatment with midostaurin also decreased splenomegaly and bone marrow mast-cell burden. Median progression-free survival was 14.1 months and median overall survival was 28.7 months (9.4 months in patients with mast-cell leukemia). The most common adverse effects of midostaurin were nausea, vomiting, and diarrhea. New or worsening grade 3 or 4 neutropenia, anemia, and thrombocytopenia occurred in >20% of patients.[2]

Rydapt is available in 25-mg capsules. For patients with AML, a 4-week treatment cycle (50 mg twice daily on days 8-21) costs $7495. For patients with advanced systemic mastocytosis, 4 weeks of treatment at 100 mg twice daily costs $29,980.[3] ■

1. RM Stone et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med 2017 Jun 23 (epub).
2. J Gotlib et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. N Engl J Med 2016; 374:2530.
3. Approximate WAC. WAC = wholesaler acquisition cost or manufacturer's published price to wholesalers; WAC represents a published catalogue or list price and may not represent an actual transactional price. Source: AnalySource®Monthly. July 5, 2017. Reprinted with permission by First Databank, Inc. All rights reserved. ©2017. www.fdbhealth.com/policies/drug-pricing-policy.

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