Midostaurin

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Approved indications: acute myeloid leukaemia, mastocytosis, mast cell leukaemia

Rydapt (Novartis)
25 mg capsules
Australian Medicines Handbook section 14.2.4, Tyrosine kinase inhibitors

Tyrosine kinases play a role in certain haematological malignancies. In about 30% of cases of acute myeloid leukaemia there is a mutation of the gene which encodes for FMS-like tyrosine kinase 3 (FLT3). A mutation in another gene (KIT) which encodes tyrosine kinase is found in most cases of systemic mastocytosis. In this rare and potentially fatal condition there is a proliferation of mast cells which can accumulate in organs and bone marrow. Its most aggressive form is mast cell leukaemia.

Midostaurin is an inhibitor of several tyrosine kinases,[1] including those related to FLT3 and KIT. It induces apoptosis in leukaemic cells and inhibits mast cell proliferation.

The capsules are taken twice daily with food to reduce nausea. Midostaurin is metabolised by cytochrome P450 (CYP) 3A4 to form active metabolites. While midostaurin has a half-life of 20 hours, one of its metabolites has a half-life of 495 hours. Most of the dose is excreted in the faeces. Midostaurin and its metabolites may induce or inhibit the metabolism of other drugs and vice versa. Strong inducers of CYP3A4, such as carbamazepine, should be avoided as they decrease the concentrations of midostaurin. No dose adjustments are recommended for patients with mild–moderate liver or kidney impairment.

The main placebo-controlled trial of midostaurin in acute myeloid leukaemia involved 717 patients with the FLT3 mutation. They were randomised to receive chemotherapy with daunorubicin and cytarabine plus midostaurin (50 mg twice daily) or placebo. After an induction and consolidation phase patients who were in remission continued midostaurin or placebo for up to twelve 28-day cycles. This full course of treatment was completed by 69 of the 360 patients taking midostaurin and 51 of the 357 in the placebo group. From the time of randomisation, the median overall survival was 74.7 months with midostaurin and 25.6 months with placebo.[2]

A small study has followed up patients with advanced systemic mastocytosis for more than 10 years (median duration of follow-up 124 months). The 26 patients had been treated with midostaurin 100 mg twice daily for up to 12 cycles of 28 days, and 18 had responded. The patients who responded could continue treatment. Their median overall survival was 41.2 months (19.2 months for non-responders).[3]

Another open-label trial in advanced systemic mastocytosis studied the same dose of midostaurin. There were 116 patients in the trial including 89 with organ damage due to mastocytosis and 16 with mast cell leukaemia. They were treated continuously in four-week cycles. The median duration of treatment was 11.4 months. There was a response in 60% of the patients which lasted for a median of 24.1 months. Responses included improvement in anaemia, thrombocytopenia and liver function. For example, eight of the 20 patients who had been dependent on red-cell transfusions were no longer dependent on them. The median overall survival was 33.9 months. In patients with organ damage it was 28.7 months and in those patients with mast cell leukaemia it was 9.4 months.[4]

The adverse effects of midostaurin are similar in acute myeloid leukaemia and systemic mastocytosis, but the frequencies are different. Febrile neutropenia affects 83.4% of patients with leukaemia, but only 7.7% of those with mastocytosis. Some of this difference may be due to the use of chemotherapy. Severe neutropenia is an indication to interrupt treatment. There were some deaths from cardiac dysfunction in patients with systemic mastocytosis, but there was no difference from the placebo group in myeloid leukaemia. Pulmonary toxicity has been reported with midostaurin monotherapy and in combination with chemotherapy. Adverse events led to midostaurin being stopped by 9.2% of the patients with leukaemia and 23.9% of those with mastocytosis. For both conditions very common adverse effects include infections, nausea, vomiting, headache, epistaxis and hyperglycaemia.

The three studies show the beneficial effects of midostaurin, but there are some questions. Acute myeloid leukaemia usually presents in older people, but the trial only included patients up to 59 years old. As 57% of the patients in this trial had an allogeneic transplant, and therefore stopped midostaurin, its benefit is less clear.[2] There is also some uncertainty in advanced systemic mastocytosis as the open-label studies were uncontrolled, however this is a rare disease with few treatment options.[4]

T manufacturer provided the product information

REFERENCES

1. Clarke SJ, Sharma R. Angiogenesis inhibitors in cancer – mechanisms of action. Aust Prescr 2006;29:9-12. https://doi.org/10.18773/austprescr.2006.007
2. Stone RM, Mandrekar SJ, Sanford BL, Laumann K, Geyer S, Bloomfield CD, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med 2017;377:454-64. https://doi.org/10.1056/NEJMoa1614359

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3. DeAngelo DJ, George TI, Linder A, Langford C, Perkins C, Ma J, et al. Efficacy and safety of midostaurin in patients with advanced systemic mastocytosis: 10-year median follow-up of a phase II trial. Leukemia 2018;32:470-8. https://doi.org/10.1038/leu.2017.234
4. Gotlib J, Kluin-Nelemans HC, George TI, Akin C, Sotlar K, Hermine O, et al. Efficacy and safety of midostaurin in advanced systemic mastocytosis. N Engl J Med 2016;374:2530-41. https://doi.org/10.1056/NEJMoa1513098

The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, the European Medicines Agency and the Therapeutic Goods Administration.