New drugs

Asciminib

Approved indication: chronic myeloid leukaemia

Scemblix (Novartis)

20 mg and 40 mg film-coated tablets

Tyrosine kinase inhibitors are the mainstay of treatment for chronic myeloid leukaemia.[1] However, patients may develop resistance to treatment and some patients do not respond to tyrosine kinase inhibitors because they have a genetic mutation (T315I). As resistance may be related to the binding site on the tyrosine kinase molecule, there has been a search for drugs that use an alternative binding site.

Asciminib is a tyrosine kinase inhibitor with a different binding site. It has also been called a STAMP inhibitor (as it specifically targets the ABL myristoyl pocket).

Depending on the dose, asciminib tablets are taken once or twice daily without food, as food reduces absorption. While most of the dose will be excreted unchanged in the faeces, asciminib is also metabolised by cytochrome P450 (CYP) 3A4. Its concentrations will therefore be increased by inhibitors of CYP3A4, such as clarithromycin and azole antifungal drugs, and decreased by inducers, such as rifampicin. Asciminib itself is an enzyme inhibitor, so it will raise concentrations of substrates of CYP3A4, such as midazolam and fentanyl, and substrates of CYP2C9, such as warfarin. Although concentrations of asciminib will be increased, no dose adjustments are recommended for patients with liver or kidney disease.

An early indication of the efficacy of asciminib came from a dose-escalation study. This involved 150 patients who had been unable to tolerate tyrosine kinase inhibitors or who had been previously treated with at least two different tyrosine kinase inhibitors. All the patients had the Philadelphia chromosome and 22% had the T315I mutation. Molecular responses were used to assess efficacy. In the patients without the T315I mutation who could be evaluated, 37% (37/99) had a major molecular response within six months. A major molecular response was achieved by 24% (4/17) of the patients with the mutation by 12 months.[2]

An open-label phase III trial studied previously treated patients with chronic myeloid leukaemia who were Philadelphia chromosome positive, but did not have a T315I mutation. One group of 157 patients was randomised to receive asciminib 40 mg twice daily while 76 took bosutinib, another tyrosine kinase inhibitor, 500 mg once daily. The median follow-up was 14.9 months with the molecular response being assessed at 24 weeks. There was a major molecular response in 25% of the patients taking asciminib and 13.2% of the bosutinib group.[3] This advantage for asciminib was still present when the patients were reviewed at 96 weeks.

A higher dose of asciminib has been tried in patients with the T315I mutation. In this open-label trial, 52 previously treated patients with chronic myeloid leukaemia were given asciminib 200 mg twice daily. Among the evaluable patients, 40.8% (20/49) had a major molecular response by 24 weeks. At 96 weeks there was a response in 46.9% (23/49).[4]

In the phase III trial, 5.8% of the patients stopped asciminib because of adverse effects compared with 21.1% of the bosutinib group.[3] A common adverse effect is myelosuppression, particularly thrombocytopenia, and this may require treatment to be withheld or stopped. Full blood counts are required every two weeks for the first three months of treatment. Serum lipase and amylase should also be monitored as some patients will develop pancreatitis. Blood pressure should be checked as hypertension is a common adverse effect. As a few patients will develop prolongation of the QT interval, the ECG should be monitored. In the trial using asciminib 200 mg twice daily there were hypersensitivity reactions in 26.9% of the patients.[4] As asciminib is likely to be harmful to the fetus, it should not be used in pregnancy.

The evidence for the safety and efficacy of asciminib is currently limited. For example, the Australian product information states that the safety profile is based on a total of 356 patients. As a molecular response is a surrogate outcome, it is too early to know if asciminib improves survival. It would also be useful to know how asciminib compares to ponatinib which is also approved for previously treated patients and those with the T315I mutation.

T manufacturer provided the product information

REFERENCES

1. Li EW, Yeung D, Fuller S. Chronic leukaemias in the community. Aust Prescr 2020;43:126-30. https://doi.org/10.18773/austprescr.2020.034
2. Hughes TP, Mauro MJ, Cortes JE, Minami H, Rea D, DeAngelo DJ. Asciminib in chronic myeloid leukemia after ABL kinase inhibitor failure. N Engl J Med 2019;381:2315-26. https://doi.org/10.1056/NEJMoa1902328

Aust Prescr 2022;45:211–2
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The new drug commentaries in *Australian Prescriber* are prepared by the Editorial Executive Committee. Some of the views expressed on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

NEW DRUGS

3. Réa D, Mauro MJ, Boquimpani C, Minami Y, Lomaia E, Voloshin S, et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. Blood 2021;138:2031-41. https://doi.org/10.1182/blood.2020009984
4. Cortes JE, Hughes TP, Mauro MJ, Hochhaus A, Rea D, Goh YT, et al. Asciminib, a first-in-class STAMP inhibitor, provides durable molecular response in patients (pts) with chronic myeloid leukemia (CML) harboring the T315I mutation: primary efficacy and safety results from a phase 1 trial. Blood 2020;136(Suppl 1):47-50. https://doi.org/10.1182/blood-2020-139677

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.