

New drugs

Axitinib

Approved indication: renal cell carcinoma

Inlyta (Pfizer)

1 mg and 5 mg tablets

Australian Medicines Handbook section 14.2.3

Axitinib is another addition to the group of tyrosine kinase inhibitors – sorafenib, sunitinib and pazopanib* – for renal cell carcinoma. Its anti-angiogenic effects stem from its inhibition of the vascular endothelial growth factor receptors 1, 2 and 3.

Early trials of axitinib in patients with refractory metastatic disease were promising.^{1,2} In a more recent open-label randomised phase III trial of 723 patients, axitinib (5 mg twice daily) was compared with sorafenib (400 mg twice daily). At enrolment, patients had progressive disease despite previous treatment with sunitinib, bevacizumab plus interferon alfa, temsirolimus or cytokines. Dose increases were allowed with axitinib (maximum 10 mg twice daily) but not with sorafenib. The patients who received axitinib survived for significantly longer without disease progression than those who received sorafenib (median of 6.7 months vs 4.7 months).³ However, overall median survival was similar between treatments (20.1 months vs 19.2 months).

The safety of axitinib seems to be comparable to sorafenib. Adverse reactions were very common, with over half of the patients in the trial having their axitinib dose reduced or interrupted because of an event. Diarrhoea (55% of patients), hypertension (40%), fatigue (39%), decreased appetite (34%), nausea (32%), dysphonia (31%) and hand-foot syndrome (27%) were the most common. In the phase III trial, 16% of patients had a bleeding event and just over a third had anaemia. Conversely, 10% of patients had increased haemoglobin so monitoring this parameter is important. Thrombocytopenia (15%), lymphopenia (33%), creatinine elevation (55%), hypocalcaemia (39%) and lipase elevation (27%) were also common. Axitinib can affect thyroid (19.2% of patients had hypothyroidism) and liver function so these should be measured at baseline and regularly during treatment.

* sorafenib – Aust Prescr 2006;29:167-71
sunitinib – Aust Prescr 2006;29:167-71
pazopanib – Aust Prescr 2010;33:193-8

High blood pressure is a problem with axitinib and should be controlled with antihypertensives. In persistent cases, the axitinib dose may need to be reduced, or interrupted then restarted at a lower dose when blood pressure has normalised. Proteinuria occurs with axitinib (10.9% of patients) and should be monitored before and during treatment.

In the axitinib arm of the phase III trial, one patient died of a cerebrovascular accident and another of pulmonary embolism. Axitinib should be used with care in patients with a history of such events, particularly as they were excluded from the trial. There was also a death from gastric haemorrhage and axitinib should not be used in patients who have recently had gastric bleeding. Gastrointestinal perforation and fistulas have been reported with axitinib and patients should be monitored for symptoms during treatment.

One patient in the trial developed reversible posterior leukoencephalopathy syndrome. It can present with headache, seizure, lethargy, confusion, blindness and other neurological symptoms, with or without hypertension. Treatment should be stopped if this is suspected.

Following an oral dose of axitinib, peak plasma concentrations are reached within four hours and steady state is achieved after 2–3 days. Axitinib is metabolised in the liver and the dose should be reduced in patients with moderate hepatic impairment. Axitinib is excreted in the faeces and urine and caution is urged in patients with end-stage renal disease.

Axitinib is metabolised mainly by cytochrome P450 (CYP) 3A4, but also by CYP1A2, CYP2C19 and UGT1A1 so there is a potential for drug interactions. Concomitant use of strong CYP3A4 inhibitors (such as ketoconazole, clarithromycin, grapefruit juice) or inducers (such as rifampicin, carbamazepine, St John's wort) may affect axitinib concentrations. If these drugs cannot be avoided, adjustment of the axitinib dose is recommended.

The prognosis for patients with advanced renal cell carcinoma is poor. Axitinib provides another option for those who have relapsed despite previous treatment. Although it may temporarily reduce disease progression, it does not seem to prolong overall survival any more than sorafenib. It is not known how axitinib will compare to other treatments for this disease.

T manufacturer provided the product information



Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data 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. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

REFERENCES *

1. Rixe O, Bukowski RM, Michaelson MD, Wilding G, Hudes GR, Bolte O, et al. Axitinib treatment in patients with cytokine-refractory metastatic renal-cell cancer: a phase II study. *Lancet Oncol* 2007;8:975-84.
2. Rini BI, Wilding G, Hudes G, Stadler WM, Kim S, Tarazi J, et al. Phase II study of axitinib in sorafenib-refractory metastatic renal cell carcinoma. *J Clin Oncol* 2009;27:4462-8.
3. Rini BI, Escudier B, Tomczak P, Kaprin A, Szczylik C, Hutson TE, et al. Comparative effectiveness of axitinib versus sorafenib in advanced renal cell carcinoma (AXIS): a randomised phase 3 trial. *Lancet* 2011;378:1931-9.

First published online 28 September 2012

Cyclizine lactate

Approved indication: prevention of postoperative nausea and vomiting

Valoid (Link Medical Products)

ampoules containing 50 mg/1 mL for injection

Australian Medicines Handbook section 1.2.1

About a third of patients will develop postoperative nausea and vomiting if they are not given prophylaxis. It is more common in women, especially after abdominal surgery.

Cyclizine, an antihistamine, is already being used (tablets and injectable solution) as an antiemetic after surgery in Australia. However, the solution for injection has only recently been approved by the Therapeutic Goods Administration.

A Cochrane review of antiemetics analysed 10 studies of parenteral cyclizine.¹ The trials were mainly in women having surgery (caesarean, laparoscopy), except for one study in boys. An analysis of these studies found that cyclizine decreased the risk of nausea by 65% and vomiting by 55%, compared to placebo. Overall, cyclizine's antiemetic effect was comparable to ondansetron. However in the study of boys having surgery for hypospadias, cyclizine was no better than placebo.²

In a trial not included in the review, cyclizine was compared to droperidol in patients administering their own analgesia after surgery. Thirty women were randomised to receive cyclizine or droperidol during surgery and then after, intravenously, with patient-controlled morphine. Nausea scores were comparable between treatments, with three patients in each group needing extra antiemetics.³

Cyclizine has also been used in combination with other antiemetics. Before anaesthesia, 960 women undergoing day surgery were given intravenous cyclizine 50 mg, intravenous granisetron 1 mg, or both. Postoperative nausea and vomiting were less common with combination treatment than with cyclizine or granisetron alone (17% vs 23% and 24%).⁴

Cyclizine's antiemetic effect lasts for approximately four hours. The elimination half-life is around 14 hours following a single 25 mg intravenous dose. Cyclizine can be given up to three times a day but treatment should not continue beyond 48 hours.

Drowsiness is common with cyclizine and it may have additive effects with alcohol and other drugs that cause nervous system depression such as hypnotics, sedatives and anaesthetics. Other adverse effects include dizziness, dry mouth, constipation, blurred vision, headache, somnolence, dyskinesia, tremor, convulsions, transient speech disorders and injection-site reactions. Disorientation, restlessness, agitation, insomnia and hallucinations have also been reported. Temporary paralysis has occasionally occurred in patients with underlying neuromuscular disorders.

Because of its anticholinergic effects, cyclizine may precipitate urinary retention and incipient glaucoma. Monitoring is recommended in patients with glaucoma, obstructive disease of the intestine, liver disease, epilepsy and prostatic hypertrophy. As cyclizine may cause thickening of bronchial secretions, it should be used with caution in patients with asthma or chronic obstructive pulmonary disease. This drug may increase the adverse effects of other anticholinergic drugs.

Cyclizine is contraindicated in patients with severe heart failure. It is a category B3 drug and its use in pregnancy and lactation is not recommended.

This drug is effective for preventing postoperative nausea and vomiting, and is comparable to other antiemetics such as ondansetron, granisetron and droperidol. Cyclizine is not recommended for children and there have been no studies in older people.

manufacturer did not respond to request for data

REFERENCES

1. Carlisle J, Stevenson CA. Drugs for preventing postoperative nausea and vomiting. *Cochrane Database Syst Rev* 2008, issue 4.
2. O'Brien CM, Titley G, Whitehurst P. A comparison of cyclizine, ondansetron and placebo as prophylaxis against postoperative nausea and vomiting in children. *Anaesthesia* 2003;58:707-11.
3. Laffey JG, Boylan JF. Cyclizine and droperidol have comparable efficacy and side effects during patient-controlled analgesia. *Ir J Med Sci* 2002;171:141-4.
4. Johns RA, Hanousek J, Montgomery JE. A comparison of cyclizine and granisetron alone and in combination for the prevention of postoperative nausea and vomiting. *Anaesthesia* 2006;61:1053-7.

First published online 11 September 2012

Velaglucerase alfa

Approved indication: Gaucher's disease type 1 VPRIV (Shire)

glass vials containing 400 units as lyophilised powder for reconstitution

Australian Medicines Handbook section: Appendix A

Gaucher's disease is one of the lysosomal storage diseases. A genetic disorder results in a lack of glucocerebrosidase. This enzyme deficiency leads to accumulation of glucocerebroside in macrophages, with enlargement of the liver and spleen. There can be bone involvement, anaemia and thrombocytopenia.

Enzyme replacement therapy has been available since the 1990s, first with alglucerase and later with the genetically engineered imiglucerase (Aust Prescr 1999;22:95-8). While imiglucerase was produced from Chinese hamster ovary cells, velaglucerase alfa is produced from human fibroblast cell lines. It has the same amino acid sequence as natural glucocerebrosidase.

As Gaucher's disease is relatively rare (only about 400 patients in Australia), the clinical trials of velaglucerase have been small. In a trial of adults with no recent use of imiglucerase, 12 symptomatic patients were given intravenous infusions of velaglucerase every other week for up to nine months. There were improvements in their haemoglobin and platelet counts. Liver and spleen volumes reduced. These improvements were sustained in nine patients who entered an extension study for an additional 39 months.¹

Two doses of velaglucerase were compared in a 12-month study in children and adults. In the 12 patients who were treated at a dose of 60 units/kg the mean haemoglobin increased from 108.3 g/L to 125.5 g/L. It increased from 107.2 g/L to 131.6 g/L in the 13 patients given 45 units/kg. Platelet counts increased by $50.88 \times 10^9/L$ with 60 units/kg and by $40.92 \times 10^9/L$ with 45 units/kg. While both doses decreased spleen volume, there was no significant decrease in liver volume.

The 60 units/kg dose has been recommended. This is given as a one hour infusion every other week. A dose reduction may be possible depending on the response.¹

A phase III study randomised 34 patients to be treated with velaglucerase 60 units/kg or imiglucerase for nine months. The patients' haemoglobin concentration was the primary outcome. Their mean haemoglobin increased by 16.2 g/L with velaglucerase and by 14.9 g/L with imiglucerase. There was also an increase in mean platelet counts and decreases in

liver and spleen volumes. These results showed that the efficacy of velaglucerase is not inferior to that of imiglucerase.

Another trial studied 40 patients who had already been treated with imiglucerase for at least 30 months. When they were switched to velaglucerase there were no significant changes in haemoglobin or platelet counts over the next 12 months.

A shortage of imiglucerase in 2009 led to patients' treatments being reduced. Some of the effects of reduced treatment were reversed in a group of 32 patients who were switched to velaglucerase. However, imaging in ten of these patients detected an increase in liver volume in five patients after six months of velaglucerase.²

The safety data for velaglucerase came from 94 adults and children. Reactions to the infusion were the most common problem. These included headache, fever, nausea, dizziness and altered blood pressure. Adverse events which were more frequent than with imiglucerase included headache, fever, diarrhoea, hypertension and arthralgia. Patients may also complain of bone pain or back pain. No data are available concerning the use of velaglucerase in pregnancy or lactation.

Some patients develop antibodies to imiglucerase. Although hypersensitivity reactions have occurred with velaglucerase, so far only one patient has developed antibodies to velaglucerase. Caution is needed if the patient is hypersensitive to other enzyme replacement products.

Enzyme replacement therapy is expensive. Although the number of patients needing therapy is small, there is now another option for treatment.

T T manufacturer provided additional useful information

REFERENCES *+A

1. Zimran A, Altarescu G, Philips M, Attias D, Jmoudiak M, Deeb M, et al. Phase 1/2 and extension study of velaglucerase alfa replacement therapy in adults with type 1 Gaucher disease: 48-month experience. *Blood* 2010;115:4651-6.
2. van Dussen L, Cox TM, Hendriks EJ, Morris E, Akkerman EM, Maas M, et al. Effects of switching from a reduced dose imiglucerase to velaglucerase in type 1 Gaucher disease: clinical and biochemical outcomes. *Haematologica* 2012 Jul 6 (Epub ahead of print). doi:10.3324/haematol.2011.059071.

First published online 28 September 2012

The T-score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2011;34:26-7.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).

A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-auspar.htm)

Erratum

Antivenom update

(Aust Prescr 2012;35:152-5)

An observant reader noticed that the photo of a tiger snake in the October issue was actually a photo of a broad-headed snake (*Hoplocephalus bungaroides*). This was an error, and here is a picture of a tiger snake (*Notechis scutatus*).



Image courtesy of Scott Eipper

EDITORIAL OFFICE

For general correspondence such as Letters to the Editor, contact the Editor.

Postal: The Editor
 Australian Prescriber
 Suite 8, 8 Phipps Close
 DEAKIN ACT 2600

Telephone: (02) 6202 3100

Fax: (02) 6282 6855

Email: info@australianprescriber.com

Website: www.australianprescriber.com

Twitter: @AustPrescriber

NEW SUBSCRIPTIONS OR CHANGES OF ADDRESS

Australian Prescriber is distributed every two months, free of charge, to medical practitioners, dentists and pharmacists in Australia, on request. It is also available on the internet free of charge.

For the paper copy or an email alert with each new issue, subscribe via any option below.



Online at
www.australianprescriber.com



Post the form below to:
Australian Prescriber Mailing Service
 GPO Box 1909
 CANBERRA ACT 2601



Phone: (02) 6241 6044
Fax: (02) 6160 3888

✓ Tick applicable:

- Send me an email alert
- Send me the paper copy
- Change my address for the paper copy
- Send me available back issues
- Stop sending the paper copy

Name: _____

Email: _____

Profession: _____
 e.g. general practitioner, resident, etc.

Reference number (on wrapper) or old address: _____

Address/new address: _____

See Privacy notice at
www.australianprescriber.com/privacynotice

A:

ANSWERS TO SELF-TEST QUESTIONS

- | | |
|---------|---------|
| 1 True | 2 False |
| 3 False | 4 True |
| 5 False | 6 True |
| 7 False | 8 False |

NPS Disclaimer

© National Prescribing Service Limited. ABN 61 082 034 393. Independent, not-for-profit and evidence based, NPS enables better decisions about medicines and medical tests. We are funded by the Australian Government Department of Health and Ageing. Reasonable care is taken to provide accurate information at the date of creation. This information is not intended as a substitute for medical advice from a qualified health professional. Health professionals should rely on their own expertise and enquiries when providing medical advice or treatment. Where permitted by law, NPS disclaims all liability (including for negligence) for any loss, damage or injury resulting from reliance on or use of this information.

Medicines Safety Update ('MSU') is produced by the Australian Government Department of Health and Ageing, Therapeutic Goods Administration. NPS has not verified the accuracy or currency of the information contained in MSU.