NEW DRUGS

New drugs

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First published 15 February 2017

Ceritinib

Approved indication: non-small cell lung cancer
Zykadia (Novartis)
150 mg capsules
Australian Medicines Handbook section 14.2.4

Ceritinib is indicated for people with advanced anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancer that has become resistant to crizotinib[1] or who cannot tolerate crizotinib. Rearrangements of the ALK gene lead to expression of oncogenic proteins which promote cell proliferation. As a tyrosine kinase inhibitor, ceritinib inhibits signalling of ALK. Up to 5% of people with non-small cell lung cancer have ALK-positive disease. These cancers are usually adenocarcinomas and are more common in non-smokers.

The approval of ceritinib is based on the results of a phase I (ASCEND-1)[2] and a phase II (ASCEND-2)[3] trial. Enrolled patients had advanced ALK-positive disease which had progressed despite other therapy. Many of them (60–71%) had brain metastases at baseline. Both trials were open-label without a control arm. Following treatment with ceritinib 750 mg once daily, 39–56% of patients had a partial or complete response, measured by regular CT and MRI scans of their tumours. Median progression-free survival was 5.7–6.9 months and median overall survival was 14.9–16.7 months (see Table).[2,3]

Diarrhoea, nausea and vomiting were very common in a safety cohort (n=525), occurring in 84%, 80% and 63% of patients respectively. Approximately 5% of these effects were serious. Grade 3 and 4 increases in liver enzymes were also very common and monitoring before and during treatment is important as dose reductions or interruptions may be required.

QT interval prolongation occurred in 6.5% of patients taking ceritinib. This was serious in some cases and the dose had to be reduced or discontinued. Ceritinib is not recommended in patients with congenital long QT syndrome or those taking drugs that prolong the QTc interval such as domperidone. Monitoring for electrolyte disorders is also important. Bradycardia was reported in 1.9% of patients and ceritinib should not be given with other drugs that have the same effect, such as beta blockers. Heart rate and blood pressure should be monitored regularly.

Severe and sometimes fatal pneumonitis has been reported with ceritinib and it was one of the most common reasons for permanent discontinuation in the trials, along with pneumonia. Other serious adverse effects included hyperglycaemia (5% of patients) and pancreatic toxicity (3%).

The recommended dose of ceritinib is 750 mg (5 capsules) taken at the same time each day. Capsules should be taken on an empty stomach (≥2 hours before or after a meal) as food increases exposure to the drug. Capsules should not be crushed or chewed.

Peak plasma concentrations are reached 4–6 hours after administration. The terminal half-life in plasma is 31–41 hours and steady state is reached after 15 days. Ceritinib is primarily metabolised by cytochrome P450 (CYP) 3A and most of the dose is excreted in the faeces. Moderate–severe hepatic impairment may increase plasma concentrations of ceritinib so the drug is not recommended in these patients.

Table **Efficacy of ceritinib in ALK-positive non-small cell lung cancer in the ASCEND trials**

Outcome	ASCEND-1[2] *	ASCEND-2[3]
Overall response rate †	56% (92 of 163 patients)	39% (54 of 140 patients)
Median duration of response	8.3 months	9.7 months
Median progression-free survival	6.9 months	5.7 months
Median overall survival	16.7 months	14.9 months

ALK anaplastic lymphoma kinase
* Results refer only to the cohort of patients who had been previously treated with an ALK-inhibitor.
† Partial and complete responses were measured by regular CT and MRI scans.

Some of the views expressed in the following notes 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.

Ceritinib is a substrate of CYP3A and P-glycoprotein. Strong CYP3A inhibitors (e.g. ketoconazole and ritonavir) can increase ceritinib concentrations, and inducers (e.g. carbamazepine, phenytoin, St John's wort) can decrease them. Concomitant use of these drugs should be avoided if possible and patients should be advised not to drink grapefruit juice. If a strong CYP3A inhibitor is needed, the ceritinib dose should be reduced by one-third. Caution is urged with inhibitors and inducers of P-glycoprotein.

Ceritinib may inhibit CYP3A and CYP2C9 directly so it can affect drugs that are metabolised by these enzymes. Doses of interacting drugs may need to be reduced and drugs with a narrow therapeutic index such as fentanyl, phenytoin and warfarin should be avoided.

The solubility of ceritinib decreases as gastric pH increases therefore antacids, proton pump inhibitors and H_2 receptor antagonists can potentially reduce ceritinib's bioavailability and effect.

Up to half of the patients in the trials responded to ceritinib and on average their response lasted around 8–9 months. However, there were no comparators in the studies so it is not known how ceritinib compares to other options. Given the drug's toxicity, the benefits of treatment need to be balanced against the risk of serious and sometimes fatal adverse effects.

[X] manufacturer did not respond to request for data

REFERENCES

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2. Kim DW, Mehra R, Tan DS, Felip E, Chow LQ, Camidge DR, et al. Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. Lancet Oncol 2016;17:452-63. http://dx.doi.org/10.1016/S1470-2045(15)00614-2
3. Crinò L, Ahn MJ, De Marinis F, Groen HJ, Wakelee H, Hida T, et al. Multicenter phase II study of whole-body and intracranial activity with ceritinib in patients with ALK-rearranged non-small-cell lung cancer previously treated with chemotherapy and crizotinib: Results from ASCEND-2. J Clin Oncol 2016;34:2866-73. http://dx.doi.org/10.1200/JCO.2015.65.5936

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 and the European Medicines Agency.

A:

ANSWERS TO SELF-TEST QUESTIONS

1 False 2 True

Correction

Long-term prescribing of new oral anticoagulants

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First published 20 February 2017

The article by Paul KL Chin and Matthew P Doogue on long-term prescribing of new oral anticoagulants (Aust Prescr 2016;39:200-4) has been corrected.

In the Table "Characteristics of oral anticoagulants", the value of excretion unchanged in urine for apixaban should read 34%, not 50%.

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