New drugs

Alectinib

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Approved indication: non-small cell lung cancer

Alcensa (Roche)
150 mg capsules
Australian Medicines Handbook section 14.2.4

Lung cancer is usually associated with heavy smoking, however some non-small cell lung cancers occur in patients who are light smokers or have never smoked. These patients may have a genetic rearrangement. In about 5% of non-small cell lung cancers there is an abnormality involving the anaplastic lymphoma kinase (ALK) gene which results in the growth of cancer cells. These cancers can be treated with tyrosine kinase inhibitors such as crizotinib, but often spread to the brain. Alectinib hydrochloride is a tyrosine kinase inhibitor which can be used for patients who have ALK-positive, locally advanced or metastatic non-small cell lung cancer, which has progressed despite treatment with crizotinib. It can also be used in patients who cannot tolerate crizotinib.

Alectinib is taken twice a day with food. The drug is highly protein bound and the concentration in the cerebrospinal fluid is similar to the unbound fraction in plasma. Alectinib is metabolised by cytochrome P450 3A4, but no dose adjustments are recommended if alectinib is taken with inducers or inhibitors of this enzyme system. As alectinib may inhibit the P-glycoprotein transporter additional monitoring is recommended for drugs such as digoxin and dabigatran. Most of the dose of alectinib is excreted unchanged in the faeces, so renal impairment is unlikely to affect clearance. There are no pharmacokinetic studies in patients with moderate or severe liver impairment.

The initial approval of alectinib appears to have been based on two open-label, phase II studies. All the patients had ALK-positive cancers (mostly adenocarcinomas) which had progressed during treatment with crizotinib. The efficacy of alectinib was assessed using the standard Response Evaluation Criteria in Solid Tumours (RECIST).

A North American trial enrolled 87 patients, including 52 with metastases in the central nervous system. After a median follow-up of 43 weeks there was a response in 51% of the patients. The median progression-free survival was 8.1 months. The response rate for patients with central nervous system disease was 40% with 25% having a complete response.[1]

An international study enrolled 138 patients, including 84 with metastases in the central nervous system. The median follow-up was 30 weeks. There was an objective response in 50% of the 122 evaluable patients and the median progression-free survival was 8.9 months. In the patients with metastases, the disease was controlled in 83% and 27% had a complete response.[2]

Tyrosine kinase inhibitors can have serious adverse effects. Two patients died of adverse events in the American trial[1] and four died in the international trial.[2] Alectinib has been associated with pneumonitis, bradycardia and hepatotoxicity. Liver function should be checked regularly. In both trials the most frequent adverse effects included constipation, fatigue, peripheral oedema and myalgia.[1,2] Creatine kinase should be checked in the first month of therapy and in patients with muscle symptoms. Patients should minimise sun exposure as alectinib may cause photosensitivity. Dose reductions or interruptions may be needed in response to adverse reactions.

Alectinib is likely to be harmful in pregnancy and lactation. Women with a male sexual partner who is taking alectinib should use highly effective contraception.

While the response rates in the uncontrolled studies suggest a benefit for alectinib, its effect on survival still needs to be established. The response to treatment can vary, for example in the international trial the objective response rate did not reach statistical significance in patients who had previously received chemotherapy.[2] An advantage over crizotinib is that alectinib can enter the central nervous system.

A phase III trial in untreated patients has recently reported that progression-free survival with alectinib is significantly longer than with crizotinib.[3] The indications for alectinib will therefore probably evolve as more data become available.

T manufacturer provided the product information

REFERENCES

1. Shaw AT, Gandhi L, Gadgeel S, Riely GJ, Cetnar J, West H, et al. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. Lancet Oncol 2016;17:234-42. https://doi.org/10.1016/S1470-2045(15)00488-X

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.

NEW DRUGS

2. Ou SH, Ahn JS, De Petris L, Govindan R, Yang JC, Hughes B, et al. Alectinib in crizotinib-refractory ALK-rearranged non-small-cell lung cancer: a phase II global study. J Clin Oncol 2016;34:661-8. https://doi.org/10.1200/JCO.2015.63.9443
3. Peters S, Camidge DR, Shaw AT, Gadgeel S, Ahn JS, Kim DW, et al.; ALEX Trial Investigators. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. N Engl J Med 2017;377:829-38. https://doi.org/10.1056/NEJMoa1704795

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.