NEW DRUGS

Acalabrutinib

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Approved indication: mantle cell lymphoma, chronic lymphocytic leukaemia

Calquence (AstraZeneca)
100 mg capsules

Acalabrutinib is an oral small-molecule drug similar to ibrutinib for B-cell malignancies. It works by binding to Bruton's tyrosine kinase and blocking signalling through the B-cell receptor and cytokine receptor pathways. This inhibits the proliferation of B cells.

This drug is indicated for mantle cell lymphoma and chronic lymphocytic leukaemia. (The approval for mantle cell lymphoma is provisional pending more trials.) The recommended dose is one capsule twice a day as monotherapy. For chronic lymphocytic leukaemia acalabrutinib can also be given in combination with obinutuzumab.

Mantle cell lymphoma

The efficacy of acalabrutinib 100 mg twice daily was investigated in an open-label, single-arm, phase II trial of 124 patients with relapsed or refractory mantle cell lymphoma. All participants had been previously treated and some had had a stem cell transplant. After a median of 15.2 months, 81% of patients had responded to treatment and 40% had a complete response. The estimated overall survival rate at 12 months was 87%.[1]

Chronic lymphocytic leukaemia

The approval of acalabrutinib for chronic lymphocytic leukaemia appears to be based on two phase III, open-label trials that have not yet been published in full. One of the trials enrolled people with previously untreated disease. They were randomised to acalabrutinib plus obintuzumab, acalabrutinib monotherapy or chlorambucil plus obinutuzmab. After a median follow-up of 28.3 months, there was less progressive disease and fewer deaths in the acalabrutinib groups than in the comparator group (see Table).

The other trial assessed efficacy in patients with relapsed or refractory disease. They received acalabrutinib monotherapy or the investigator's choice of idelalisib plus rituximab or bendamustine plus rituximab. After a median follow-up of 16.1 months, there was less disease progression with acalabrutinib than with the comparator, but the number of deaths were similar (see Table).

Pharmacology and drug interactions

Following oral administration, peak plasma concentrations of acalabrutinib and its active metabolite (ACP-5862) are reached within an hour. The median terminal half-life of the active metabolite is 6.9 hours and most of the dose is excreted in the

Table **Efficacy of acalabrutinib in chronic lymphocytic leukaemia***

Patients with previously untreated disease			
	Acalabrutinib plus obintuzumab (179 patients)	**Acalabrutinib monotherapy (179 patients)**	**Chlorambucil plus obinutuzumab (177 patients)**
Progressive disease	5%	11.2%	46.3%
Death	2.8%	3.4%	6.2%
Estimated progression-free survival at 24 months	92.7%	87.3%	46.7%
ORR	93.9%	85.5%	78.5%

Patients with relapsed or refractory disease		
	Acalabrutinib monotherapy (155 patients)	**Investigator's choice† (155 patients)**
Progressive disease	12.3%	38.1%
Death	5.2%	5.8%
Estimated progression-free survival at 15 months	82.6%	54.9%
ORR	81.3%	75.5%

* based on data in the product information
† idelalisib plus rituximab or bendamustine plus rituximab
ORR objective response rate estimated as the number of complete and partial responses divided by the total number of patients

faeces. The drug is mainly metabolised by cytochrome P450 (CYP) 3A enzymes so co-administration with strong CYP3A inhibitors (e.g. itraconazole) and inducers (e.g. rifampicin) increase the risk of toxicity or reduce the efficacy of acalabrutinib and should be avoided. Dose adjustment of acalabrutinib may be needed with moderate CYP3A inhibitors such as erythromycin. Drugs that increase the pH of the stomach can decrease acalabrutinib concentrations. Proton pump inhibitors should be avoided and H_2-receptor antagonists should only be used two hours after the acalabrutinib dose. Antacids should be dosed separately by at least two hours.

Adverse events

The most common adverse effects with acalabrutinib in the trials included headache (22–40% of patients), diarrhoea (18–39%), fatigue (10–28%), muscle pain (15–37%) and bruising (12–34%). Cytopenias were very common and included neutropenia (21%), anaemia (10%) and thrombocytopenia (7%). Serious bleeding occurred in 3.6% of patients receiving acalabrutinib and one patient died. Concomitant use of antithrombotic drugs should therefore be avoided with acalabrutinib.

Atrial fibrillation was a concerning adverse effect with the related drug ibrutinib. In the combined safety cohort of the acalabrutinib trials, 1% of patients had grade 3 atrial fibrillation and 3% had milder events. ECG is recommended if patients develop palpitations, dizziness, syncope, chest pain or dyspnoea.

Infections were frequently reported in the chronic lymphocytic leukaemia trials and affected 57–69% of patients receiving acalabrutinib. Pneumonia was the most commonly reported serious infection. Hepatitis B reactivation and progressive multifocal leukoencephalopathy have also occurred with acalabrutinib.

Conclusion

Acalabrutinib seems to benefit patients with mantle cell lymphoma and chronic lymphocytic leukaemia. For both indications, over 80% of patients in the trials responded to treatment. In chronic lymphocytic leukaemia, acalabrutinib was associated with longer progression-free survival compared to the comparator treatments. It is not yet clear if the drug improves overall survival. Adverse effects are common and sometimes serious so may limit treatment.

T manufacturer provided the AusPAR and the product information

REFERENCE

1. Wang M, Rule S, Zinzani PL, Goy A, Casanovas O, Smith SD, et al. Acalabrutinib in relapsed or refractory mantle cell lymphoma (ACE-LY-004): a single-arm, multicentre, phase 2 trial. Lancet 2018;391:659-67. https://doi.org/10.1016/S0140-6736(17)33108-2

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 and the Therapeutic Goods Administration.