New drugs

Obinutuzumab

Approved indication: chronic lymphocytic leukaemia

Gazyva (Roche)

1000 mg/40 mL concentrate solution for infusion

Australian Medicines Handbook section 14.2.1

Chronic lymphocytic leukaemia is the most common leukaemia in adults and usually occurs in older age. It is characterised by an accumulation of abnormal B lymphocytes and median survival is 8–10 years. Current treatments include chlorambucil, cyclophosphamide, fludarabine, alemtuzumab (Aust Prescr 2006;29:167–71) and rituximab.

Obinutuzumab is a humanised monoclonal antibody. Like rituximab, it is specific for the CD20 transmembrane antigen on the surface of B lymphocytes. Binding of obinutuzumab to this antigen is thought to cause cell death by antibody-dependent phagocytosis and cellular cytotoxicity.

In a randomised open-label study, obinutuzumab added to chlorambucil was investigated in 781 previously untreated people with chronic lymphocytic leukaemia who required treatment. They had enlarged lymph nodes or spleen, thrombocytopenia and anaemia, or symptomatic disease.[1] Their median age was 73 years (39–90 years) and their median creatinine clearance was 62 mL/minute. Most of the patients had more than three comorbidities – vascular, cardiac, nutritional, gastrointestinal and metabolic disorders were the most common.

Patients were randomised into three treatment groups – chlorambucil plus obinutuzumab, chlorambucil plus rituximab, and chlorambucil alone. One arm of the trial compared chlorambucil and obinutuzumab with chlorambucil alone and the other arm compared chlorambucil and obinutuzumab with chlorambucil and rituximab. Patients receiving chlorambucil alone whose disease progressed during or after treatment were allowed to cross over to the chlorambucil plus obinutuzumab group.

Treatment was given in six 28-day cycles. The first cycle consisted of an intravenous infusion of obinutuzumab 1000 mg on days 1, 8 and 15. In the next five cycles obinutuzumab was only given on day 1. Chlorambucil was given on day 1 and 15 in all treatment cycles.

After six cycles of treatment, obinutuzumab plus chlorambucil prolonged progression-free survival by 15 months compared to chlorambucil alone, and by 11 months compared to rituximab plus chlorambucil. More patients had a complete or partial response to the obinutuzumab combination than to chlorambucil alone (see Table). Median overall survival times in the trial were not reached.[1]

The most common adverse events with obinutuzumab were infusion-related reactions. These occurred in two-thirds of people, mostly during the first infusion, and included nausea, chills, hypotension, fever, vomiting, dyspnoea, flushing, hypertension, headache, tachycardia and diarrhoea. Bronchospasm, throat irritation, wheezing and atrial fibrillation also occurred. To reduce infusion reactions, giving the first obinutuzumab infusion slowly in two doses over two days is recommended. Also, antihypertensive drugs should be withheld 12 hours before the infusion and one hour after. Although premedication with a corticosteroid, analgesic and antihistamine is also recommended, it only modestly reduced infusion-related reactions in the trial.[1] As tumour lysis syndrome has also been reported, prophylactic

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.

Table **Efficacy of obinutuzumab added to chlorambucil in chronic lymphocytic leukaemia** [1]

	Comparison 1		Comparison 2	
	Chlorambucil plus obinutuzumab	**Chlorambucil alone**	**Chlorambucil plus obinutuzumab**	**Chlorambucil plus rituximab**
Number of patients	238	118	333	329
Estimated median progression-free survival	26.7 months	11.1 months	26.7 months	15.2 months
Patients with a complete response‡	22.3%	0%	20.7%	7%
Patients with a partial response‡	55%	31.4%	57.7%	58.1%

‡ response was measured three months after the end of six treatment cycles

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allopurinol and adequate hydration before the infusion are recommended for people with a high tumour burden or high lymphocyte count.

Other common adverse events with obinutuzumab included neutropenia (41% of people) and thrombocytopenia (15.4%). Some patients may need granulocyte colony-stimulating factor for their neutropenia.

Infections are common with obinutuzumab (38% of people). The drug should not be given during an active infection and caution is urged in patients with a chronic or recurring infection. Fatal cases of progressive multifocal leukoencephalopathy have been reported with obinutuzumab and patients with neurological symptoms require further investigation. Hepatitis B virus reactivation has also occurred and has been fatal in some cases. Patients should be screened before starting treatment and carriers of the hepatitis B virus should be monitored during and for at least 12 months after treatment. Obinutuzumab should be discontinued if hepatitis develops. Live vaccines are not recommended.

Worsening heart problems such as arrhythmias, angina, acute coronary syndrome, myocardial infarction and heart failure have occurred with this drug. Some cases resulted in death. Patients with a pre-existing heart condition should be closely monitored, especially during infusions.

After infusion, obinutuzumab is cleared by catabolism. After six cycles of treatment, the elimination half-life is approximately 30 days. Some patients developed antibodies to obinutuzumab (8/140). This did not seem to affect their clinical response and they did not develop anaphylactic or hypersensitivity reactions.

Obinutuzumab appears to benefit patients with chronic lymphocytic leukaemia. However, infusion-related reactions are common so prophylactic measures are recommended. Fatal infections, including progressive multifocal leukoencephalopathy, have also occurred and patient monitoring is important. It is not yet known if obinutuzumab will prolong overall survival compared to other treatments.

[T][T][T] manufacturer provided clinical evaluation

REFERENCE *†A

1. Goede V, Fischer K, Busch R, Engelke A, Eichhorst B, Wendtner CM, et al. Obinutuzumab plus chlorambucil in patients with CLL and coexisting conditions. N Engl J Med 2014;370:1101-10.

First published online 13 August 2014

The Transparency score ([T]) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

* 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)