Ofatumumab

Approved indication: B cell chronic lymphocytic leukaemia

Arzerra (GlaxoSmithKline)

100 mg/5 mL and 1000 mg/50 mL concentrate for infusion

Australian Medicines Handbook section 14.2.1

Chronic lymphocytic leukaemia is the most common adult leukaemia and is characterised by an accumulation of abnormal B lymphocytes. Ofatumumab adds to the growing number of treatments for this disease, including bendamustine (Aust Prescr 2014;37:214-21), chlorambucil, fludarabine (Aust Prescr 1995;18:86-7), rituximab (Aust Prescr 1999;22:20-3) and alemtuzumab (Aust Prescr 2006;29:167-71).

Ofatumumab is a human monoclonal antibody. Like rituximab, it binds to an epitope of CD20, which is expressed on B lymphocytes and B cell tumours. Binding to CD20 is thought to cause cell death mainly through complement-dependent cytotoxicity and antibody-dependent cell-mediated cytotoxicity.

Ofatumumab is approved for two indications in chronic lymphocytic leukaemia:

- first line in combination with chlorambucil or bendamustine for people who cannot have fludarabine
- as monotherapy for refractory disease.

First-line treatment when fludarabine cannot be given

In an open-label trial, ofatumumab added to chlorambucil was compared with chlorambucil alone in 447 previously untreated patients in whom fludarabine was contraindicated (e.g. due to age or comorbidities). They received treatment for a maximum of twelve 28-day cycles or for a minimum of three months. Ofatumumab was given intravenously (300 mg on day 1 and 1000 mg on day 8 for the first cycle, followed by 1000 mg on day 1 of subsequent cycles) and chlorambucil was given orally (10 mg/m^2 on days 1–7 of each cycle). Progression-free survival was statistically longer with ofatumumab and chlorambucil compared to chlorambucil alone (22.4 months vs 13.1 months). The overall response rate was also higher with combination treatment than with chlorambucil alone (82% vs 69%). This trial is currently unpublished.

In a single-arm trial, the same dose of ofatumumab was combined with bendamustine (90 mg/m^2 intravenously on days 1–2 of each 28-day cycle) in 44 previously untreated people who could not have fludarabine. After a median of six cycles, almost all patients had responded with 43% of them having a complete response. This trial has also not yet been published.

Refractory disease

Ofatumumab monotherapy is also approved for patients whose disease is refractory to fludarabine and alemtuzumab. Survival of these patients is often less than a year. In an open-label dose-escalation study, 33 patients were given weekly intravenous infusions for four weeks. There were three different ofatumumab regimens – one 100 mg dose followed by three 500 mg doses (3 patients), one 300 mg dose followed by three 1000 mg doses (3 patients), or one 500 mg dose followed by three 2000 mg doses (27 patients).[1] After 19 weeks, one patient in the lowest dose group and 13 patients in the highest dose group had a partial remission. Although two patients maintained their response until week 27, the others had progressive disease. Overall, the median progression-free survival was approximately 3.5 months.

By the end of treatment, malignant B cells in peripheral blood had decreased by a median of 97% (15–100%) in patients given the highest ofatumumab dose. Normal B cells were also depleted and this was sustained until week 24, after which cell numbers started to increase.[1]

In another trial, the efficacy of ofatumumab was assessed in a subset of 59 patients with disease refractory to fludarabine and alemtuzumab. Participants were given eight weekly infusions then monthly infusions for four months (first dose of 300 mg followed by 2000 mg doses). After 24 weeks, 58% of these patients had responded to treatment – all were partial responses. Median progression-free survival was 5.7 months (4.5–8 months) and median overall survival was 13.7 months.[2]

Safety and precautions

In 138 people who received monotherapy for refractory disease, almost two-thirds had an infusion-related reaction to ofatumumab. These were mostly mild to moderate and occurred during the first and second infusion. Other common adverse events included infection (67% of patients), cough (18%), diarrhoea (16%), anaemia (16%), fatigue (15%), fever (15%), neutropenia (15%), dyspnoea (13%), nausea (11%) and rash (10%). Overall, 37 of the infections were serious and 13 that started during treatment led to death. Six deaths were due to sepsis, five to pneumonia, one to *Fusarium* infection and one to progressive multifocal leukoencephalopathy.[2]

In 261 people who received ofatumumab with chlorambucil or bendamustine, neutropenia was

the most common event (31%) and was serious in most cases. Nausea (25%), rash (25%), fever (22%), diarrhoea (17%), fatigue (16%), cough (15%), pruritus (13%), vomiting (12%), dyspnoea (11%), headache (10%) and urticaria (10%) were also frequently reported.

As with monotherapy, infusion-related reactions were very common during the first cycle of combination therapy and were the reason for stopping treatment in 3% of patients. Because of this risk, which can include serious effects such as respiratory and cardiac problems, premedication with an analgesic, an antihistamine and a corticosteroid is recommended, particularly at the beginning of therapy. The first and second infusions should be given more slowly, starting at 12 mL/hour. The rate can be increased later if reactions do not occur.

As cytopenias are common, blood counts (including platelets) should be monitored regularly. Because ofatumumab reduces the number of B lymphocytes, there is an increased risk of infection. Neurological symptoms such as confusion, dizziness, loss of balance, difficulty with walking or talking could be a sign of progressive multifocal leukoencephalopathy and should be investigated further. There is also a risk of hepatitis B reactivation, so people with evidence of previous infection should be monitored during and for 6–12 months after treatment. Live vaccines are not recommended.

Conclusion

Ofatumumab as monotherapy for refractory disease, or in combination with chlorambucil or bendamustine when fludarabine cannot be given, seems to prolong progression-free survival in people with chronic lymphocytic leukaemia. Premedication is recommended to reduce infusion-related reactions, particularly at the beginning of treatment. Prescribers should be aware that progressive multifocal leukoencephalopathy can occur with this drug.

T manufacturer provided the product information

REFERENCES *†A

1. Coiffier B, Lepretre S, Pedersen LM, Gadeberg O, Fredriksen H, van Oers MH, et al. Safety and efficacy of ofatumumab, a fully human monoclonal anti-CD20 antibody, in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: a phase 1-2 study. Blood 2008;111:1094-100.
2. Wierda WG, Kipps TJ, Mayer J, Stilgenbauer S, Williams CD, Hellmann A, et al. Ofatumumab as single-agent CD20 immunotherapy in fludarabine-refractory chronic lymphocytic leukemia. J Clin Oncol 2010;28:1749-55.

First published online 20 April 2015

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).