New drugs

Brentuximab vedotin

Approved indication: Hodgkin lymphoma, anaplastic large cell lymphoma

Adcetris (Takeda)

vials containing 50 mg powder for injection

Australian Medicines Handbook section 14.2.1

Brentuximab vedotin consists of an anti-CD30 antibody conjugated to a cytotoxic drug called monomethylauristatin E (MMAE). The cytotoxic part disrupts the microtubule network in cells and causes apoptosis. This drug is indicated for patients with relapsed or refractory classic Hodgkin lymphoma (including after autologous stem cell transplant) and systemic anaplastic large cell lymphoma. CD30 is selectively expressed on the surface of lymphoma cells in both of these diseases.

Maximum concentrations of the antibody–drug conjugate are reached at the end of a 30-minute intravenous infusion and its terminal half-life is 4–6 days. The antibody portion is thought to be catabolised and a fraction of the cytotoxic portion – MMAE – is metabolised and excreted in the urine and faeces. A lower starting dose should be considered in patients with hepatic impairment or severe renal impairment and close monitoring is recommended.

The anti-CD30 antibody on its own has minimal efficacy – in a trial of 72 people with relapsed or refractory CD30-positive lymphomas, only six responded.[1] However, conjugating the antibody to a cytotoxic drug improved antitumour activity. In a single-arm, open-label phase II trial, 75% of patients with relapsed or refractory Hodgkin lymphoma responded to brentuximab vedotin (see Table).[2] All of these patients had previously had an autologous transplant. In a similarly designed trial in relapsed or refractory systemic anaplastic large cell lymphoma, 86% of patients had a response to brentuximab vedotin (see Table).[3] Just over a quarter of the participants had previously had an autologous transplant.

Infection was the most common adverse event in the trials, occurring in 61% of people. In 16% of cases, infection was thought to be related to the study drug. Serious infections included pneumonia, staphylococcal bacteraemia, sepsis and herpes zoster. The opportunistic infections *Pneumocystis jirovecii* pneumonia and oral candidiasis also occurred.

The most common drug-related adverse effects included peripheral sensory neuropathy (44%), fatigue (42%), nausea (41%), diarrhoea (34%), neutropenia (21%) and vomiting (20%). Some of these were serious – neutropenia and peripheral sensory neuropathy resulted in delayed or reduced dosing. Other serious drug reactions included thrombocytopenia, constipation, diarrhoea, vomiting, fever, peripheral motor neuropathy, hyperglycaemia, demyelinating polyneuropathy, tumour lysis syndrome and Stevens-Johnson syndrome.

Table **Efficacy of brentuximab vedotin in two trials** [2,3]

	Intravenous brentuximab vedotin 1.8 mg/kg every 3 weeks ‡	
Patient response	Hodgkin lymphoma (102 patients)	Refractory systemic anaplastic large cell lymphoma (58 patients)
Complete remission	34% (35 patients)	57% (33 patients)
Partial remission	40% (41 patients)	29% (17 patients)
Stable disease	22% (22 patients)	3% (2 patients)
Progressive disease	3% (3 patients)	5% (3 patients)
Not evaluable	1% (1 patient)	2% (1 patient)
Median duration of complete responses	20.5 months	13.2 months
Median progression-free survival	5.6 months	13.3 months
Median overall survival	22.4 months	not reached

‡ patients could have up to a maximum of 16 infusions

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.

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Some adverse events were fatal including sepsis, acute pancreatitis and progressive multifocal leukoencephalopathy. Treatment should be stopped if any of these are suspected.

Anaphylaxis has been reported to occur during and after the infusion. This was more common in people with antibodies to the study drug (approximately a third of patients).

Co-administration of strong inhibitors of cytochrome P450 (CYP) 3A4 and P-glycoprotein (e.g. ketoconazole) increases exposure to MMAE so may increase the risk of adverse effects such as neutropenia. The concomitant use of brentuximab vedotin with bleomycin causes pulmonary toxicity and is contraindicated.

Brentuximab vedotin has the potential to cause fetal harm and is not recommended during pregnancy. There are no data for its use during lactation. Animal toxicity studies indicated that this drug may affect reproductive function and fertility in males. Men are advised to have sperm frozen before treatment and avoid fathering a child during and for six months after treatment.

Brentuximab vedotin seemed to be effective in advanced Hodgkin lymphoma and anaplastic large cell lymphoma, with 34–57% of patients achieving complete remission. However, the trials were small and there were no comparators. Adverse effects can be severe and sometimes fatal and are likely to limit treatment dose and duration. There are no safety data for this drug beyond 12 months of treatment.

T manufacturer provided the AusPAR

REFERENCES *†A

1. Ansell SM, Horwitz SM, Engert A, Khan KD, Lin T, Strair R, et al. Phase I/II study of an anti-CD30 monoclonal antibody (MDX-060) in Hodgkin's lymphoma and anaplastic large-cell lymphoma. J Clin Oncol 2007;25:2764-9.
2. Younes A, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J Clin Oncol 2012;30:2183-9.
3. Pro B, Advani R, Brice P, Bartlett NL, Rosenblatt JD, Illidge T, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. J Clin Oncol 2012;30:2190-6.

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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)