NEW DRUGS

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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.

Daratumumab

Approved indication: multiple myeloma

Darzalex (Janssen-Cilag)
vials containing 100 mg in 5 mL or 400 mg in 20 mL concentrate

Multiple myeloma is a malignant proliferation of plasma cells. They produce monoclonal paraproteins (M proteins). The proliferation in the bone marrow causes skeletal damage and the paraproteins can cause kidney failure. Advances in therapy such as bone marrow transplants and drugs such as bortezomib and lenalidomide have improved the prognosis, but most patients eventually relapse. This has led to a search for new targets for drug therapy. One of these targets is the CD38 glycoprotein which is found on myeloma cells. Daratumumab is a monoclonal antibody that binds to CD38 and leads to the death of the cells.

The drug is diluted and given as an intravenous infusion. The half-life increases with repeated and increasing doses and it takes many weeks to reach a steady-state serum concentration. The drug is cleared in a similar way to other antibodies. Liver and renal disease have no significant effects on the pharmacokinetics of daratumumab. The molecule may interfere with some laboratory investigations, such as the Coombs test.

The clinical trials of daratumumab have involved patients who had been previously treated for multiple myeloma. Efficacy was assessed according to the criteria of the International Myeloma Working Group.

The approval of daratumumab monotherapy appears to be based on two open-label, uncontrolled, phase II trials.[1,2] There was a total of 148 patients in the pooled analysis of these trials.[3] The patients had received a median of five previous treatments and most of them had disease that was refractory to immunomodulatory drugs and proteasome inhibitors, such as bortezomib. After a median treatment duration of 3.4 months, the overall response rate was 31.1%, including four patients with a complete response. The median duration of the response was 7.6 months with a median overall survival of 20.1 months.[1] Based on the results of these studies, the recommended regimen for monotherapy is a weekly infusion for eight weeks, followed by every two weeks, until 24 weeks, then monthly until the disease progresses.

This regimen was used in a phase III, open-label, randomised controlled trial, which studied daratumumab in combination with lenalidomide and dexamethasone in 286 patients who had received at least one previous treatment. Their outcomes were compared with those of 283 patients who were treated with lenalidomide and dexamethasone. The overall response rate for those taking daratumumab was 92.9% compared with 76.4% in the control group. There was a complete response in 43.1% of the daratumumab group and 19.2% of the control group. When the results were reported, the median progression-free survival had not been reached with the daratumumab combination, but was 18.4 months with lenalidomide and dexamethasone.[4]

Daratumumab has also been studied in combination with bortezomib and dexamethasone. In this phase III, open-label, randomised controlled trial, daratumumab was given every three weeks, rather than fortnightly, from weeks 10–24 of the regimen. The patients had all received at least one previous treatment for myeloma. In the 251 patients randomised to receive the combination, the overall response rate was 82.9% compared with 63.2% in the 247 patients who received bortezomib and dexamethasone. The respective complete response rates were 19.2% and 9.0%. The median progression-free survival was not reached with the combination, but was 7.2 months in the control group.[5]

As the CD38 glycoprotein is also found on haemopoietic cells, daratumumab's effects are not limited to cancer cells. It is very common for patients to develop anaemia, neutropenia and thrombocytopenia, so the full blood count must be monitored during treatment.

Approximately half of the patients in the trials had infusion-related reactions, so pre-medication is required. Corticosteroids are also recommended for two days after the infusion to reduce the risk of delayed reactions.

In the studies of monotherapy only 4.1% of the patients discontinued daratumumab because of adverse events. The most frequent adverse effects were fatigue, nausea and anaemia.[3]

Adverse events which were more frequent when daratumumab was added to lenalidomide and dexamethasone included neutropenia, diarrhoea and cough. Discontinuations due to adverse events were slightly less frequent than

in the control group (6.7% vs 7.8%).[4] There was a similar result when daratumumab was given with bortezomib and dexamethasone (7.4% vs 9.3%). In that trial, the combination caused more haematological adverse events than the control group and it was also associated with a higher rate of peripheral neuropathy.[5]

Daratumumab improves the response to treatment, particularly when used in combination with lenalidomide (see Table). However, its effect on longer term survival needs further study. While combination therapy is currently limited to patients who have relapsed after at least one other therapy, and monotherapy is restricted to those who have had at least three therapies, the optimum approach to treatment needs to be studied. Trials are underway to assess the role of daratumumab earlier in the disease.

T T manufacturer provided additional useful information

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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.

Table **Efficacy of daratumumab in multiple myeloma**

Trial	Treatment	Number of patients	Median duration of follow-up (months)	Overall response rate	Proportion of patients without disease progression at 12 months	Overall survival at 12 months
GEN501[1]	Monotherapy	42 (16 mg/kg group)	10.2	36%	65% (of 15 responders)	77%
SIRIUS[2]	Monotherapy	106	9.3	29.2%	–	64.8%
POLLUX[4]	Daratumumab, lenalidomide and dexamethasone	286	13.5	92.9%	83.2%	92.1%
	Lenalidomide and dexamethasone	283		76.4%	60.1%	86.8%
CASTOR[5]	Daratumumab, bortezomib and dexamethasone	251	7.4	82.9%	60.7%	–
	Bortezomib and dexamethasone	247		63.2%	26.9%	–