New drugs

Pomalidomide

Approved indication: multiple myeloma
Pomalyst (Celgene)
1 mg, 2 mg, 3 mg and 4 mg capsules
Australian Medicines Handbook section 14.2.4

Multiple myeloma is characterised by abnormal plasma cells in the bone marrow. The disease is generally considered incurable and most patients eventually become refractory to treatment. Pomalidomide is indicated for those who have already received at least two treatments, including bortezomib (Aust Prescr 2006;29:84-7) and lenalidomide (Aust Prescr 2008;31:49-55). Median overall survival in this group is around nine months with treatment and three months without treatment.

Pomalidomide is structurally related to thalidomide and lenalidomide. Its exact mechanism of action is unknown, but like other drugs in the class, it is thought to have antimyeloma, anti-angiogenic, immunomodulatory and stromal cell effects. In a phase II trial, the efficacy of pomalidomide was enhanced when given with low-dose dexamethasone (see Table).[1]

The approval of pomalidomide is mainly based on an open-label phase III trial which enrolled patients who had relapsed or progressed despite a median of five previous treatments. Participants were randomised to 28-day cycles of pomalidomide with low-dose dexamethasone (302 patients), or to high-dose dexamethasone alone (153 patients). Treatment was continued until disease progressed or patients developed unacceptable toxicity. After 10 months, pomalidomide and low-dose dexamethasone was found to significantly improve response rates, progression-free and overall survival compared to high-dose dexamethasone (see Table).[2]

After a median follow-up of 10 months, most people had discontinued treatment (80% of the pomalidomide group, 93% of the comparator group). Progressive disease was the most common reason for stopping, but approximately 10% of people discontinued because of an adverse event.[2]

Serious adverse events, defined as resulting in hospitalisation, disability or incapacity, occurred in 61% of patients in the pomalidomide group and 53% of those in the comparator group. The most common adverse events of any grade with pomalidomide were infections (68% of people), anaemia (52%),

Table **Efficacy of pomalidomide‡ in relapsed or refractory multiple myeloma**

Phase II trial [1]		
Outcomes (after a median of 14 months of follow-up)	**Pomalidomide plus low-dose dexamethasone§** (108 patients)	**Pomalidomide monotherapy** (113 patients)
Median progression-free survival	4.2 months	2.7 months
Median overall survival	16.5 months	13.6 months
Overall response	33% (3% were complete responses)	18% (2% were complete responses)
Phase III trial [2]		
Outcomes (after a median of 10 months of follow-up)	**Pomalidomide plus low-dose dexamethasone§** (302 patients)	**High-dose dexamethasone#** (153 patients)
Median progression-free survival	4 months	1.9 months
Median overall survival	12.7 months	8.1 months
Overall response	31% (1% were complete responses)	10% (no complete responses)

‡ pomalidomide 4 mg/day was taken orally on days 1–21 of a 28-day cycle
§ dexamethasone 40 mg once a week during each 28-day cycle
# dexamethasone 40 mg given on days 1–4, 9–12 and 17–20 of a 28-day cycle. Dose reduced to 20 mg in people aged 75 years and older.

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.

neutropenia (51%), fatigue (34%), thrombocytopenia (30%), fever (27%), diarrhoea (22%) and constipation (22%).[2] Peripheral neuropathy occurred in 12% of patients. Adverse events were more likely to occur during the first two cycles of treatment. There were 11 treatment-related deaths with pomalidomide – eight cases of infections, two cases of multi-organ failure or sudden death, and one nervous system disorder.[2]

Because of its structural similarity to thalidomide, pomalidomide is contraindicated in pregnancy. It is available under a restricted distribution program, which includes measures to prevent pregnancy. Women should be using a recommended form of contraception and have a negative pregnancy test before starting pomalidomide and men must use a condom throughout treatment, even if they have had a vasectomy.

Regular monitoring of blood counts is recommended with pomalidomide because anaemia, neutropenia and thrombocytopenia are so common and patients often need their dose reduced or interrupted. Dizziness and confusion have been reported and patients should be warned not to drive or operate machinery if this occurs.

Deep vein thrombosis occurs with pomalidomide so prophylaxis is recommended in patients with a high risk. There is no experience of this drug in patients with significant heart problems such as congestive heart failure, recent myocardial infarction or poorly controlled angina, as they were excluded from trials. Close monitoring is recommended in patients with an increased risk of tumour lysis syndrome (those with a high tumour burden or renal impairment).

Following oral administration, maximum plasma concentrations are reached after 2–3 hours. Pomalidomide's plasma half-life is 7.5 hours in patients with multiple myeloma. After metabolism in the liver, the drug is eliminated in the urine (73%) and faeces (15%). It is unclear if the dose needs to be reduced in renal disease as patients with moderate to severe impairment were excluded from the trials. Patients with hepatic impairment (serum bilirubin >34.2 micromol/L) and elevated transaminases (>3 x upper limit of normal) were also excluded.

Pomalidomide is predominantly metabolised by cytochrome P450 (CYP) 1A2 and 3A4 and is also a substrate of P-glycoprotein. Co-administration of strong CYP1A2 inhibitors, such as fluvoxamine, may increase pomalidomide exposure and monitoring is recommended. Close monitoring is also advised in patients taking concomitant warfarin as there is a potential drug interaction with dexamethasone.

For patients with few options left, pomalidomide with low-dose dexamethasone may offer longer progression-free and overall survival compared to treatment with high-dose dexamethasone. However, haematological toxicity and infections are very common and may limit treatment.

T T manufacturer provided additional useful information

REFERENCES *†

1. Richardson PG, Siegel DS, Vij R, Hofmeister CC, Baz R, Jagannath S, et al. Pomalidomide alone or in combination with low-dose dexamethasone in relapsed and refractory multiple myeloma: a randomized phase 2 study. Blood 2014;123:1826-32.
2. San Miguel J, Weisel K, Moreau P, Lacy M, Song K, Delforge M, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol 2013;14:1055-66.

First published online 14 November 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)