NEW DRUGS

Aust Prescr 2018;41:56–7
https://doi.org/10.18773/austprescr.2018.019
First published 27 February 2018

Carfilzomib

Approved indication: multiple myeloma

Kyprolis (Amgen)
vials containing 30 mg and 60 mg powder
Australian Medicines Handbook section 14.1.8

Carfilzomib is a new intravenous drug for multiple myeloma. It is indicated for people with relapsed or refractory disease after at least one previous therapy. It should be given in combination with dexamethasone or with lenalidomide and dexamethasone.

Like bortezomib, carfilzomib is a proteasome inhibitor. It works by interfering with the system for breaking down proteins within cells. As cancer cells are rapidly multiplying, inhibiting proteasomes causes proteins to accumulate. In in vitro and animal studies, this slows cell growth and eventually causes cell death.

The approval of carfilzomib is based on two randomised open-label trials – ASPIRE[1] and ENDEAVOR.[2] The trials enrolled people who had been treated with 1–3 previous therapies.

In the ASPIRE study, carfilzomib with lenalidomide and dexamethasone was compared to lenalidomide and dexamethasone alone for 18 treatment cycles. Patients who had previously progressed on bortezomib or lenalidomide with dexamethasone, or had previously discontinued lenalidomide and dexamethasone because of an adverse effect, were not allowed in the trial.[1]

The progression-free survival of patients was longer when carfilzomib was added to lenalidomide and dexamethasone compared with those given lenalidomide and dexamethasone alone (26.3 vs 17.6 months, p=0.0001). Also more patients in the carfilzomib arm had at least a partial response to treatment (87.1 vs 66.7%, p<0.001) (see Table).

Diarrhoea (42.3% vs 33.7%), thrombocytopenia (29.3% vs 22.9%), cough (28.8% vs 17.7%), fever (28.6% vs 20.8%), upper respiratory tract infection (28.6% vs 19.5%), hypokalaemia (27.6% vs 13.4%), hypertension (14.5% vs 7.5%), and headache (13.5% vs 8%) were more common with carfilzomib than with the comparator.[1]

In the ENDEAVOR study, carfilzomib plus dexamethasone was compared to bortezomib plus dexamethasone. Although patients who had previously been treated with carfilzomib or bortezomib were allowed in the trial, they must have had at least a partial response to the treatment before relapse and not discontinued because of an adverse effect.[2]

As in the ASPIRE trial, progression-free survival was significantly longer in the carfilzomib arm compared with the comparator (18.7 vs 9.4 months, p<0.0001). Overall response rates were also higher (76.9 vs 62.6%, p<0.0001) (see Table).[2]

Anaemia (40.8% vs 27.6% of patients), fever (31.3% vs 14.7%), dyspnoea (30.5% vs 13.2%), hypertension (29.8% vs 9.6%), cough (26.1% vs 14.9%), muscle spasms (19.7% vs 6.1%), and bronchitis (21.4% vs 10.1%) were more frequent with carfilzomib than with bortezomib.[2]

Cardiac failure (7%) was reported with carfilzomib in the trials, as was myocardial infarction (2%) and myocardial ischaemia (1%). Some of these cases were fatal. Other serious and potentially life-threatening adverse events with carfilzomib include pulmonary and hepatic toxicities, pulmonary hypertension, dyspnoea, hypertension, acute renal failure, tumour lysis syndrome, infusion reactions, thrombocytopenia, posterior reversible encephalopathy syndrome and thrombotic microangiopathy. Patients need to be closely monitored during treatment and the dose of

Table **Efficacy of carfilzomib in multiple myeloma**

Study	Treatment (no. of patients)	Median progression-free survival	Overall response rate*
ASPIRE[1]	Carfilzomib with lenalidomide + dexamethasone (396 patients)	26.3 months	87.1% (31.8% had a complete response or better)
	Lenalidomide + dexamethasone (396 patients)	17.6 months	66.7% (9.3% had a complete response or better)
ENDEAVOR[2]	Carfilzomib + dexamethasone (464 patients)	18.7 months	76.9% (12.5% had a complete response or better)
	Bortezomib + dexamethasone (465 patients)	9.4 months	62.6% (6.2% had a complete response or better)

* Overall response rate was defined as the proportion of patients achieving a partial response or better.

carfilzomib may need to be reduced or stopped until symptoms have resolved. Checking hydration, fluid requirements and electrolytes is important.

This drug is not recommended during pregnancy and contraception should be used during treatment. There are no data in humans but carfilzomib caused embryo-fetal toxicity in pregnant rabbits. It is not known if the drug is excreted in breast milk.

Carfilzomib is administered in 28-day cycles. An intravenous infusion is given on two consecutive days each week for three weeks followed by a 12-day rest period. After administration, carfilzomib is rapidly metabolised by peptidase cleavage and epoxide hydrolysis and the inactive metabolites are excreted in the urine. On the basis of preliminary data, interactions with other medicines are not expected.

Consider giving patients antiviral prophylaxis to prevent herpes zoster infection. Thromboprophylaxis is recommended in patients also receiving lenalidomide and dexamethasone depending on their risk.

More than 75% of pre-treated patients appeared to respond to carfilzomib when given as combination therapy. However, it is not yet known if it will extend survival. Toxicity may limit treatment and fatal reactions can occasionally occur so monitoring is paramount.

TT manufacturer provided additional useful information

REFERENCES

1. Stewart AK, Rajkumar SV, Dimopoulos MA, Masszi T, Špička I, Oriol A, et al; ASPIRE Investigators. Carfilzomib, lenalidomide and dexamethasone for relapsed multiple myeloma. N Engl J Med 2015;372:142-52. https://doi.org/10.1056/NEJMoa1411321
2. Dimopoulos MA, Moreau P, Palumbo A, Joshua D, Pour L, Hájek R, et al; ENDEAVOR Investigators. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOUR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol 2016;17:27-38. https://doi.org/10.1016/S1470-2045(15)00464-7

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.

A:

ANSWERS TO SELF-TEST QUESTIONS

1 False 2 False

EDITORIAL OFFICE

For general correspondence such as Letters to the Editor, contact the Editor.

Postal The Editor
Australian Prescriber
PO Box 104
DEAKIN WEST 2600

Telephone (02) 6202 3100

Fax (02) 6282 6855

Email info@australianprescriber.com

Website nps.org.au/australianprescriber

Twitter @AustPrescriber

SUBSCRIPTIONS

Australian Prescriber is published every two months online. All content is accessible free of charge in full text at nps.org.au/australianprescriber. New drugs are published between issues as they become available.

An email alert can be sent to you when *Australian Prescriber* publishes new material. Subscribe or update your details at nps.org.au/australianprescriber

For back issues, and copies of the Anaphylaxis wallchart and Switching-antidepressants poster, email info@australianprescriber.com