Carfilzomib and Dexamethasone (CarDex)

Indication

Relapsed multiple myeloma for patients who have had only one previous line of therapy (that did not include bortezomib).

(NICE TA457)

ICD-10 codes

Codes with a pre-fix C90

Regimen details

Cycle 1

Day	Drug	Dose	Route
1 and 2	Carfilzomib	20 mg/m^2 (maximum 44mg)	IV infusion
8 and 9, 15 and 16	Carfilzomib	56 mg/m^2 (maximum 123mg)	IV infusion
1 and 2, 8 and 9, 15 and 16, 22 and 23	Dexamethasone*	20mg OM	PO/IV

Cycle 2 onwards

Day	Drug	Dose	Route
1 and 2, 8 and 9, 15 and 16	Carfilzomib	56 mg/m^2 (maximum 123mg)	IV infusion
1 and 2, 8 and 9, 15 and 16, 22 and 23	Dexamethasone*	20mg OM	PO/IV

* Dexamethasone should be administered 30 minutes to 4 hours before carfilzomib.

Cycle frequency

28 days

Number of cycles

Until disease progression or unacceptable toxicity.
Consider a once weekly dosing schedule to help manage toxicity.

Administration

Pre and post hydration:

Cycle 1, day 1: Oral hydration of 30mL/kg/day from 48 hours prior to commencing treatment is recommended. Pre- hydration with 250-500ml sodium chloride 0.9% IV is recommended with each dose during cycle 1. Consider additional post-hydration with 250-500mL sodium chloride 0.9%. For subsequent cycles consider pre- and post-hydration if LDH or uric acid is elevated and / or patient is considered at risk for tumour lysis syndrome.

Encourage oral fluid intake of 1L before and after each dose of carfilzomib to maintain adequate hydration.

Carfilzomib is administered in 50-100mL glucose 5% by IV infusion over 30 minutes. Flush line with 5% glucose solution immediately before and after administration.

Patients should be monitored for infusion related reactions, for 1 hour following each carfilzomib infusion during cycle 1 and following cycle 2 day 1 and thereafter if required.

Dexamethasone is available as 500microgram and 2mg tablets. The dose should be taken in the morning, with or after food, 30 minutes to 4 hours before carfilzomib administration. Alternatively dexamethasone may be administered as an IV bolus.

Pre-medication

Dexamethasone as above.

Emetogenicity

This regimen has low emetogenic potential.

Additional supportive medication

H_2 antagonist or proton pump inhibitor.
Allopurinol 300mg OD (100mg OD if CrCl< 20mL/min) for patients with a high tumour burden, for cycles 1 and 2.
Bisphosphonates as per local policy.
Laxatives if required.
Antifungal, antiviral and PCP prophylaxis as per local policy.
Thromboprophylaxis should be considered based on an individual benefit/risk assessment.

Extravasation

Carfilzomib is neutral (group 1).

Investigations – pre first cycle

Investigation	Validity period
FBC and film	14 days
Clotting screen	14 days
U+Es (including creatinine)	14 days
LFTs	14 days
Glucose	14 days
Blood pressure (lying and standing)	Prior to cycle 1
Clinical assessment for cardiac disease. Consider ECG +/- echocardiogram in those with a history of cardiac disease or over 70 years of age.	Prior to cycle 1

Serum electrophoresis (or alternative biological measure of response if M protein not measurable).
Bone marrow aspirate and trephine.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC*	72 hours
U+Es (including creatinine)*	72 hours
LFTs	72 hours
Blood pressure	On day 1
Glucose	As clinically indicated.

Serum electrophoresis (or alternative biological measure of response if M protein not measurable).

*Monitor FBC and renal function weekly before treatment in cycles 1 and 2 and subsequently if dose level adjustment for toxicity has been made.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 75 x 10^9/L
Creatinine clearance	≥ 30mL/min (see below)
Bilirubin	< ULN
ALT/AST	< ULN
Non-haematological toxicity	Resolved to ≤ grade 1

Dose modifications

Carfilzomib:

Dose level	**Carfilzomib dose**
Full dose	56mg/m^2
First dose reduction	45mg/m^2
Second dose reduction	36mg/m^2
Third dose reduction	27mg/m^2
Continued toxicity	Consider once weekly dosing; consider discontinuation

- **Haematological toxicity**

Treatment on day 1 of each cycle should only be initiated if neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 75 x 10^9/L. If cytopenia is considered to be disease related, treatment may be given at consultant discretion.

For subsequent doses within each cycle:

Haematological toxicity	**Recommended action**
Neutrophils < 0.5 x 10^9/L	Withhold treatment. Once recovered to ≥ 0.5 x 10^9/L, continue at same dose level For subsequent drops to < 0.5 x 10^9/L, withhold treatment and consider recommencing with 1 dose level reduction.
Febrile neutropenia (Neutrophils < 0.5 x 10^9/L and an oral temperature > 38.5°C or two consecutive readings of > 38.0°C for 2 hours)	Withhold treatment. If neutrophil count returns to baseline grade and fever resolves, resume at the same dose level
Platelet count < 10 x 10^9/L or evidence of bleeding with thrombocytopenia	Withhold treatment. Once recovered to ≥ 10 x 10^9/L and bleeding is controlled resume with same dose level For subsequent drops to < 10 x 10^9/L, withhold treatment and consider recommencing with 1 dose level reduction.

- **Renal impairment**

No starting dose adjustment for carfilzomib is recommended for baseline mild, moderate, or severe renal impairment or patients on chronic dialysis. However, in phase 3 clinical studies, the incidence of adverse events of acute renal failure was higher in patients with lower baseline creatinine clearance than that among patients with higher baseline creatinine clearance.

Renal toxicity	Recommended action
Serum creatinine equal to or greater than 2 × baseline	Withhold carfilzomib and monitor renal function. Resume carfilzomib when renal function has recovered to within 25% of baseline. Consider resuming at 1 dose level reduction. For patients on dialysis receiving carfilzomib, the dose is to be administered after the dialysis procedure.
Creatinine clearance < 15 mL/min (or creatinine clearance decreases to ≤ 50% of baseline) or need for dialysis	

- **Hepatic impairment**

The pharmacokinetics of carfilzomib has not been evaluated in patients with severe hepatic impairment. No starting dose adjustment is recommended in patients with mild or moderate hepatic impairment based on available pharmacokinetic data. However, higher incidence of hepatic function abnormalities, ≥ grade 3 adverse events and serious adverse events have been reported in patients with mild or moderate baseline hepatic impairment compared with patients with normal hepatic function.

- **Other toxicities**

Hypertension: including hypertensive crisis and hypertensive emergency, have been observed. Some of these events have been fatal. All patients should be routinely evaluated for hypertension and treated as needed.

Pulmonary Toxicity: including Acute Respiratory Distress Syndrome, acute respiratory failure, and acute diffuse infiltrative pulmonary disease: Withhold carfilzomib and evaluate promptly

Dyspnoea: For severe or life threatening dyspnoea, withhold carfilzomib and evaluate.

All other grade 3 or 4 non-haematological toxicities: Withhold carfilzomib until resolved or returned to baseline. Recommence with 1 dose level reduction.

Dexamethasone:

Suggested dexamethasone dose reductions if required:

Dose level	Dexamethasone dose
Full dose	20mg OM
Dose level -1	12mg OM
Dose level -2	8mg OM

Dexamethasone is usually discontinued following 2 dose reductions.

Dexamethasone dose modifications:

Toxicity	Grade	Dose Modification
Dyspepsia	Grade 1-2	Maintain dose and treat with H2 antagonist or PPI as per local policy. Reduce dose one level if symptoms persist.
	≥ Grade 3	Withhold until symptoms return to baseline. Add H2 antagonist or PPI as per local policy and resume with one dose level reduction.
Oedema	≥ Grade 3	Withhold until symptoms return to baseline. Use diuretics as needed and resume with one dose level reduction.
Confusion or mood alteration	≥ Grade 2	Withhold until symptoms resolve. Resume with one dose level reduction.
Muscle weakness	≥ Grade 2	Withhold until muscle weakness ≤ Grade 1. Resume with one dose level reduction.
Hyperglycaemia	≥ Grade 3	Withhold until treated with insulin or oral hypoglycaemic agents as needed. Resume with one dose level reduction.
Acute pancreatitis		Discontinue dexamethasone.
Other dexamethasone adverse events	≥ Grade 3	Withhold until resolved to ≤ Grade 2. Resume with one dose level reduction.

Adverse effects - for full details consult product literature/ reference texts

The incidence of adverse events (including cardiac failure) in clinical trials was higher for patients who were ≥ 75 years of age compared to patients who were < 75 years of age.

- **Serious side effects**

Myelosuppression
Cardiac disorders, QT prolongation.
Acute respiratory distress syndrome (ARDS), interstitial lung disease.
Pulmonary hypertension
Hypertension, including hypertensive crisis and hypertensive emergency
Posterior reversible encephalopathy syndrome (PRES)
Acute renal failure
Tumour lysis syndrome
Infusion related reactions
Venous thromboembolic events
Thrombotic microangiopathy
Haemorrhage
Hepatic toxicity

- **Frequently occurring side effects**

Dyspnoea. Evaluate dyspnoea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes.
Myelosuppression
Diarrhoea, constipation
Pyrexia
Nausea and vomiting
Fatigue
Peripheral neuropathy

Headache
Hypertension
Arthralgia, muscle spasms
Hypokalaemia
Hypophosphatemia

- **Other side effects**

Significant drug interactions – for full details consult product literature/ reference texts

Carfilzomib is primarily metabolised via peptidase and epoxide hydrolase activities, and as a result, the pharmacokinetic profile of carfilzomib is unlikely to be affected by concomitant administration of cytochrome P450 inhibitors and inducers.

Carfilzomib is a P-glycoprotein (P-gp) substrate. Carfilzomib inhibits the efflux transport of digoxin, by 25%. Caution should be observed when carfilzomib is combined with substrates of P-gp (e.g. digoxin, colchicine).

Additional comments

Contraception

Female patients of child bearing potential (and/or their partners) must use effective contraception measures during and for one month following treatment. Male patients must use effective contraception measures during and for 3 months following treatment if their partner is pregnant or of childbearing potential and not using effective contraception.

Sodium content

Carfilzomib contains 0.3 mmols (7 mg) of sodium per mL of reconstituted solution. This should be taken into consideration for patients on a controlled sodium diet.

References

- Summary of Product Characteristics: Cafilzomib (Amgen Ltd) accessed 18 July 2017 via www.medicines.org.uk
- National Institute for Clinical Excellence. Technology Appraisal Guidance NICE TA457. Accessed 18 July 2017 via www.nice.org.uk
- Dimpopoulos M. et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. The Lancet Oncology, Volume 17, Issue 1, 27 – 38. http://dx.doi.org/10.1016/S1470-2045(15)00464-7
- Amgen Data on File: ENDEAVOR Clinical Study Report, pages 58-59.

Written/reviewed by: Dr A Whiteway (Consultant Haematologist, North Bristol NHS Trust)

Checked by: Sarah Murdoch (Senior Oncology/Haematology Pharmacist, SW Clinical Network)

Authorised by: Dr J Braybrooke (Consultant Oncologist, SW Clinical Network)

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