

CARFILZOMIB /DEXAMETHASONE (CarDex)

INDICATIONS

Multiple myeloma at first relapse [NICE TA657]

Requires Blueteq approval

TREATMENT INTENT

Disease modification

PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:
 - FBC & film
 - Clotting screen
 - U&Es
 - LFTs
 - Calcium
 - Albumin
 - Uric acid
 - CRP
 - Baseline random blood glucose level
 - Virology : HIV, Hepatitis B (including core antibody), and Hepatitis C
 - Calculated creatinine clearance (CrCl), urine protein/ creatinine ratio
 - Electrophoresis and immunofixation for quantitation of serum paraprotein and immunoglobulins
 - Serum free light chain assay (Freelite)
 - Hevylite analysis (if paraprotein level difficult to quantify)
 - β 2 microglobulin
 - LDH
 - Myeloma FISH should be performed in all patients at diagnosis, and in selected patients at relapse/progression to help guide treatment decisions Samples should be sent to
 - Wessex Regional Genetics Laboratory
 - **Salisbury NHS Foundation Trust**
 - **Salisbury District Hospital**
 - **Salisbury**
 - **Wiltshire, SP2 8BJ**
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 - Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle
 - Group and save
 - Imaging as per NICE/network guidance and clinical presentation

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Additional Investigations

- Plasma viscosity if hyperviscosity suspected.
- If allogeneic transplant an option: Tissue typing of patient and siblings and CMV serology.
- 2. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given.
- 3. Fertility - all patients should be offered fertility advice, as appropriate.
- 4. Hydration - fluid intake of at least 3 litres /day should be attempted.
- 5. Document patient’s height and weight, dose on actual body weight.
- 6. Document patient’s performance status.
- 7. Treatment must be agreed at the relevant MDT.

REGIMEN SPECIFIC INVESTGATIONS

- Evaluate for presence of cardiac issues in all patients, especially in those >60, history of hypertension, prior cardiac arrhythmias or IHD. Clinical assessment, Echocardiogram and ECG are mandatory in all patients to have a baseline assessment of cardiac function
- Baseline lying and standing blood pressure should be recorded prior to administration of cycle #1. Ensure BP well controlled prior to starting therapy

DRUG REGIMEN

Pre- and Post-Hydration	<p>Cycle 1 (all carfilzomib days) and Cycle 2 Day 1: pre- and post-hydration with 500ml sodium chloride 0.9% is recommended.</p> <p>Subsequent doses: pre- and post- IV hydration is recommended if lactate dehydrogenase (LDH) or uric acid is elevated and / or patients considered at risk for TLS. In other patients, encourage at least 1L oral fluids before and after each carfilzomib dose to maintain adequate hydration.</p>		
Dexamethasone	All Cycles	<p>Day 1, 2, 8, 9, 15, 16, 22 and 23</p> <p>20mg PO Daily. Dexamethasone should be given at least 30 minutes prior to carfilzomib.</p>	
Carfilzomib*	Cycle 1	<p>Day 1 and 2</p> <p>20mg/m² IV infusion in 100 mL Glucose 5% over 30 minutes (max 44mg*)</p>	<p>Patient must be monitored for 1 hour following carfilzomib infusions during cycle 1 and on cycle 2 day 1.</p>
		<p>Day 8, 9, 15 and 16</p> <p>56mg/m² IV infusion in 100mL Glucose 5% over 30 minutes (max 123mg*)</p>	
	Cycle 2 onwards	<p>Day 1, 2, 8, 9, 15 and 16</p> <p>56mg/m² IV infusion in 100mL Glucose 5% over 30 minutes (max 123mg*)</p>	

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*Doses capped at BSA 2.2m²

*Consider dosing Carfilzomib weekly, rather than twice weekly in selected patients when there are toxicity concerns. If this approach is followed, generally recommend giving days 1 &2 in cycle one, then move to weekly dosing. This can be up-titrated if poor response and no toxicity

CYCLE FREQUENCY

Repeat every 28 days until disease progression or unacceptable toxicity.

DOSE MODIFICATIONS

Prior to initiating a new cycle of therapy:

- Platelets $\geq 50 \times 10^9/L$ and ANC $\geq 1.0 \times 10^9/L$
- Non-haem toxicities should resolve to G1 or baseline

Carfilzomib dose reductions levels

Starting Dose	1 st level dose reduction	2 nd level dose reduction	3 rd level dose reduction
56 mg/m ²	45 mg/m ²	36 mg/m ²	27 mg/m ² *

* If toxicity does not resolve, discontinue treatment

Toxicity	Posology modification or delay
Haematological toxicity during a cycle	
<ul style="list-style-type: none"> • If Absolute neutrophil count $< 0.5 \times 10^9 /L$ 	Withhold carfilzomib dose, If recovered to $\geq 0.5 \times 10^9/L$, continue at the same dose level. For subsequent drops to $< 0.5 \times 10^9/L$, follow the same recommendations as above and consider 1 dose level reduction when restarting carfilzomib
<ul style="list-style-type: none"> • If platelet $\leq 10 \times 10^9/L$ or evidence of bleeding with thrombocytopenia 	Withhold carfilzomib dose. If platelet recovers to $\geq 10 \times 10^9/L$ and/or bleeding is controlled, continue at the same dose level. For subsequent drops to $< 10 \times 10^9 /L$, follow the same recommendations as above and consider 1 dose level reduction when restarting Carfilzomib.

Carfilzomib:

Renal	Hepatic
Based on PK studies; No starting dose adjustment is recommended in patients with	Mild or moderate impairment: Based on PK studies, no starting dose adjustment is

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<p>baseline mild, moderate, or severe renal impairment or patients on chronic dialysis.</p> <p>The incidence of adverse events of acute renal failure maybe higher in patients with lower baseline creatinine clearance. Monitor renal function closely is patients with CrCL < 30 mL/min.</p> <p>For patients on dialysis receiving carfilzomib, the dose is to be administered after the dialysis procedure.</p>	<p>recommended in patients with mild or moderate hepatic impairment 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. Monitor closely.</p> <p>Severe impairment: The pharmacokinetics of carfilzomib has not been evaluated in patients with severe hepatic impairment.</p>
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INVESTIGATIONS (at the beginning of each cycle unless otherwise noted)

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle
- FBC
- U&E, LFTs, Ca⁺⁺
- Blood pressure
- Ig's, paraprotein, Freelite assay.
- Consider repeat BM aspirate and trephine after 3 cycles in non-secretory myeloma and check result prior to starting cycle #5.
- Blood pressure
- Consider blood glucose monitoring in patients with diabetes and those with signs of glucose intolerance

CONCURRENT MEDICATIONS

- Allopurinol 300 mg daily for 7 days for cycle 1 only. Aim to start day before chemotherapy.
- Prophylactic aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl<10ml/min)
- Prophylactic fluconazole 50mg OD.
- Consider prophylactic co-trimoxazole 960mg OD on M/W/F if heavily pre-treated or previous autograft.
- Proton pump inhibitor or H2 antagonist at clinician's discretion.
- Bone protection as per NCCN Bone Protection protocol MM.3

EMETIC RISK

Low

EXTRAVASATION RISK:

Carfilzomib is not known to be a vesicant. There are no data available regarding skin

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corrosion/irritation or extravasation. Follow institution’s guideline on management of extravasation events in the event of carfilzomib extravasation.

MHRA alert: risk of reactivation of hepatitis B virus:

<https://www.gov.uk/drug-safety-update/carfilzomib-kyprolis-risk-of-reactivation-of-hepatitis-b-virus>

- Hepatitis B virus reactivation has been reported in patients treated with carfilzomib
- Screen all patients for hepatitis B virus before initiation of carfilzomib; patients with unknown serology who are already on treatment should also be screened
- Consider prophylaxis with antivirals for patients with positive serology who are treated with carfilzomib
- Monitor patients with positive serology for clinical and laboratory signs of hepatitis B reactivation during and after treatment
- Advise patients with positive serology to seek medical help immediately if they experience signs and symptoms suggestive of hepatitis B virus reactivation
- In patients who have hepatitis B reactivation, it is recommended to consult relevant experts when making decisions regarding hepatitis B virus treatment and the continuation, interruption, or resumption of carfilzomib

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The most common adverse events occurring in patients treated with carfilzomib and dexamethasone in ENDEAVOR trial: , anaemia, thrombocytopenia, neutropaenia, hypertension, peripheral oedema, upper respiratory tract infections, , diarrhoea, fatigue, , pyrexia, dyspnea, , cough, upper respiratory tract infection, pneumonia and hypokalemia.

- **Cardiac toxicities** include cardiac failure and myocardial infarction with fatal outcome, and myocardial ischemia. Withhold Carfilzomib and evaluate promptly. Monitor patients for evidence of volume overload and adjust fluid management/hydration as indicated
- **Pulmonary Hypertension:** Withhold Carfilzomib and evaluate
- **Dyspnoea:** commonly reported in patients treated with carfilzomib. Evaluate dyspnoea to exclude cardiopulmonary conditions including cardiac failure and pulmonary syndromes For grade 3 and 4 dyspnoea , withhold Carfilzomib and evaluate.
- **Hypertension** including hypertensive crisis: Monitor blood pressure regularly. If hypertension cannot be adequately controlled, a risk-benefit decision on continued Carfilzomib therapy is needed.
- **Acute Renal Failure:** Monitor serum creatinine regularly. Risk is higher in subjects with lower baseline creatinine clearance.
- **Tumor Lysis Syndrome (TLS):** Administer pre-treatment hydration and appropriate TLS prophylaxis. Monitor for TLS, including uric acid levels and treat promptly.
- **Pulmonary Toxicity:** including Acute Respiratory Distress Syndrome, acute respiratory failure, and acute diffuse infiltrative pulmonary disease: Withhold Carfilzomib and evaluate promptly
- **Infusion Reactions:** Symptoms may include fever, chills, arthralgia, myalgia, facial

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flushing, facial oedema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. These reactions can occur immediately following or up to 24 hours after administration. Pre-medicate with dexamethasone.

- **Thrombocytopenia:** Monitor platelet counts; interrupt or reduce Carfilzomib dosing as clinically indicated.
- **Hepatic Toxicity** and Hepatic Failure: Monitor liver enzymes. Withhold Carfilzomib if suspected.
- Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS). Monitor for signs and symptoms of TTP/HUS. Discontinue Carfilzomib if suspected.
- Posterior reversible encephalopathy syndrome (PRES): Consider neuro-radiological imaging (MRI) for onset of visual or neurological symptoms; discontinue Carfilzomib if suspected.
- Dexamethasone related toxicities include: mood changes, restlessness, withdrawal effects, glucose intolerance.

TREATMENT RELATED MORTALITY

< 5%

REFERENCES

1. Angen. Summary of Product Characteristics Kyprolis. Updated 02 May 2019.
2. Siegel DS, Martin T, Wang M, et al. A phase 2 study of single-agent carfilzomib (PX-171-003-A1) in patients with relapsed and refractory multiple myeloma. Blood 2012; 120:2817-25.
3. Vij R, Wang M, Kaufman JL, et al. An open-label, single-arm, phase 2 (PX-171-004) study of single-agent carfilzomib in bortezomib-naive patients with relapsed and/or refractory multiple myeloma. Blood 2012; 119:5661-70.
4. Dimopoulos MA 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. Lancet Oncology 2016; 17(1):27-38
5. Brinthen et al. Prevention, monitoring and treatment of cardiovascular adverse events in myeloma patients receiving carfilzomib A consensus paper by the European Myeloma Network and the Italian Society of Arterial Hypertension. J Intern Med. 2019 Jul;286(1):63-74. doi: 10.1111/joim.12882

REVIEW

Name	Revision	Date	Version	Review date
Dr Karthik Ramasamy (Consultant) Cheuk-kie Cheung (Haematology Pharmacist)	New Document	July 2017	1.0	July 2019
Network Protocol Review	Indication. Investigations. Dosing regimen. Cycle	June 2018	1.1	June 2020

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	frequency. Extravasation info. Dose modifications. Concurrent medication. Adverse events.			
Myeloma Protocol Review 2019	Update of pre and post-hydration, references	June 2019	1.2	June 2020
Faouzi Djebbari Advanced Haem Pharmacist	MHRA alert	Dec 2019	1.3	June 2020
NSSG Myeloma Group	Updated NICE TA657	Dec 2020	1.4	June 2021
Quality Manager	Nursing care plan added	May 2021	1.5	June 2021

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Nursing Care Plan Carfilzomib Dexamethasone

Indication: First relapsed multiple myeloma in bortezomib naïve patients

Frequency: 28 day cycles until disease progression or unacceptable toxicity.

Alopecia: No

CARFILZOMIB: proteasome inhibitor

Administered as IV infusion on **days 1, 2, 8, 9, 15, 16** over 30 minutes. Carfilzomib comes in 5% glucose bags but is compatible to be flushed with 0.9% normal saline.

On cycle 1 and cycle 2 day 1 patients will have pre and post hydration either side of the Carfilzomib infusion (500mls 0.9% normal saline over 1 hour pre and post).

After cycle 2 day 1 pre and post hydration (at least 1 litre) can be taken orally as long as the patient's biochemistry profile is stable and there is no risk of TLS.

Classification of extravasation: Not vesicant (There are no data available regarding skin corrosion/irritation or extravasation).

Emetic risk: low.

Side effects: anaemia, thrombocytopenia, neutropenia, hypertension, peripheral oedema, upper respiratory tract infections, diarrhoea, fatigue, pyrexia, dyspnoea, cough, upper respiratory tract infection, pneumonia and hypokalaemia.

Dosing reaction: fever, chills, arthralgia, myalgia, facial flushing, facial oedema, vomiting, weakness, shortness of breath, hypotension, syncope, chest tightness, or angina. **These reactions can occur immediately following or up to 24 hours after administration.**

DEXAMETHASONE: corticosteroid tablets

Administered orally on the day of each carfilzomib dose and the day after. Taken with or after food preferably at breakfast. Carfilzomib is given at least 30 minutes pre Carfilzomib infusion.

Side effects: restlessness, insomnia, mood changes, gastritis, hyperglycaemia, increased appetite, fluid retention, weight gain, immunosuppression.

Regime Specific Considerations:

- Baseline lying and standing blood pressure should be recorded prior to administration of cycle #1. Ensure BP well controlled prior to starting therapy and throughout. Baseline ECG required.
- Carfilzomib can be given weekly, rather than twice weekly in selected patients when there are toxicity concerns.
- Patients should attempt to drink 3 litres of water a day.
- Bloods (including glucose level) are required at the start of each cycle. Patients with unstable blood counts may require more frequent monitoring.
- Pregnancy test for pre-menopausal women under the age of 55 before the start of each cycle.

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