CARFILZOMIB /DEXAMETHASONE (CarDex)

INDICATIONS

Multiple myeloma at first relapse [NICE TA657]

Requires Blueteq approval

TREATMENT INTENT

Disease modification

PRE-ASSESSMENT

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)
- LDH
- Consider bone marrow aspirate and trephine (with immunophenotyping for kappa/lambda if appropriate) to confirm relapse, particularly if FISH data required for treatment decision support.
- 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 (address below)
- 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

Wessex Regional Genetics Laboratory
Salisbury NHS Foundation Trust
Salisbury District Hospital
SalisburyWiltshire, SP2

Additional Investigations

1. Plasma viscosity if hyperviscosity suspected.
2. If allogeneic transplant an option: Tissue typing of patient and siblings and CMV serology.
3. 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.
4. Fertility - all patients should be offered fertility advice, as appropriate.
5. Hydration - fluid intake of at least 3 litres /day should be attempted.
6. Document patient's height and weight, dose on actual body weight.
7. Document patient's performance status.
8. Treatment must be agreed at the relevant MDT.

REGIMEN SPECIFIC INVESTGATIONS

- Evaluate for presence of cardiac issues in all patients, especially in those >60yo, history of hypertension, prior cardiac arrhythmias or IHD. Clinical assessment, Echocardiogram and ECG are recommended 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

All carfilzomib doses should be capped at BSA 2.2m^2.

Patients should attempt to drink 3 litres of fluid 24 hours before, and on treatment days and avoid sugary or caffeine-based drinks where clinical situation permits.

Cycle 1:

Drug	Dose	Days	Administration
Pre and post hydration	500ml sodium chloride 0.9%	1, 2, 8, 9, 15 and 16	IVI Before and after dosing
Dexamethasone	20 mg OD	1, 2, 8, 9, 15, 16, 22, 23	Oral 30mins before carfilzomib as pre-med when due
Carfilzomib	20 mg/m^2 – max. 44mg	1 and 2	IVI over 30mins in 100mL 5% glucose **Monitor patient for 1hr following infusion**
	56 mg/m^2 – max. 123mg	8, 9, 15 and 16	

IVI= Intravenous infusion

Cycle 2 onwards:

Drug	Dose	Days	Administration
Pre and post hydration*	500ml sodium chloride 0.9%	Cycle 2 Day 1 only	IVI Before and after dosing
	Minimum 1L oral hydration	2, 8, 9, 15, 16, 22, 23	Oral Before and after dosing
Dexamethasone	20 mg OD	1, 2, 8, 9, 15, 16, 22, 23	Oral 30mins before carfilzomib as pre-med when due
Carfilzomib	56 mg/m^2 – max dose 123mg*	1, 2, 8, 9, 15, 16	IVI over 30mins in 100mL 5% glucose **Cycle 2 Day 1 only, monitor patient for 1hr following infusion**

IVI= Intravenous infusion

* **Pre- and post- IV hydration** should continue if patient is still considered at risk for TLS. In other patients, encourage at least 1L oral fluids before and after each carfilzomib dose to maintain adequate hydration.

CYCLE FREQUENCY

Repeat every 28 days until disease progression or unacceptable toxicity.

DOSE MODIFICATIONS

Prior to initiating a new cycle of therapy:

- Platelets ≥ 50 x 10^9/L and ANC ≥ 1.0 x 10^9/L
- Non-haem toxicities should resolve to G1 or baseline.

Carfilzomib dose reduction levels

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

A once weekly dosing schedule can also be considered for toxicity management. *If toxicity does not resolve after reducing to 27 mg/m^2, discontinue carfilzomib. (unfunded)

Haematological toxicity	Recommended action
ANC < 0.5 x10^9 /L *ANC= Absolute neutrophil count*	1st occurrence - Withhold carfilzomib dose. If recovered to ≥ 0.5 x10^9/L, continue at the same dose level. Subsequent occurrences - Withhold carfilzomib dose, consider 1 dose level reduction when restarting carfilzomib.
Platelets ≤ 10 x 10^9/L or evidence of bleeding with thrombocytopenia	1st occurrence - Withhold carfilzomib dose. If platelet recovers to ≥ 10 x10^9/L and/or bleeding is controlled, continue at the same dose level.

	Subsequent occurrences - Withhold carfilzomib dose, consider 1 dose level reduction when restarting Carfilzomib.

Renal dose modifications (starting treatment)	
No dose adjustment is recommended for any grade of renal dysfunction at initiation. In patients with CrCl <30ml/min cautiously monitor renal function; adverse events are more likely. Follow dose reductions as below.	
Renal dose modifications (during treatment)	
Serum creatinine greater than, or equal to 2 x baseline (i.e., AKI Stage 2 or above), and/or	Withhold carfilzomib. Resume when renal function has recovered to within 25% of baseline and consider resuming at 1 dose level reduction. If toxicity does not resolve after a 15mg/m^2 dose reduction, consider discontinuing carfilzomib. For patients on dialysis receiving carfilzomib, the dose is to be administered after the dialysis procedure.
CrCl less than 15ml/min (or creatinine clearance decreases to ≤ 50% of baseline), and/or need for dialysis	

Hepatic Adjustments	
Mild/moderate impairment	No starting dose adjustment is recommended. A higher incidence of hepatic function abnormalities, ≥ grade 3 adverse events and serious adverse events have been reported compared with patients with normal hepatic function. Monitor closely.
Severe impairment	No information available.

Dexamethasone

There are no recommended dose modifications for dexamethasone. Intolerance to steroid side-effects (e.g., insomnia, agitation, indigestion, acid reflux), or a pre-emptive reduction in the elderly, may be managed by a trial of dose reduction to 10mg, and possibly lower if stable disease at clinician discretion.

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
- Igs, 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

- Cycle 1 only - Allopurinol 300 mg OD for 7 days.
- Aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl<10ml/min)
- Fluconazole 50mg OD.
- Consider co-trimoxazole 960mg OD on M/W/F if heavily pre-treated or previous autograft. Reduction to 480mg can be considered if persistent low WCC/neutrophil counts.
- Consider levofloxacin prophylaxis at 500mg PO OD for 12 weeks (i.e. cycles 1-3). Beware tendonitis risk.
- H2 antagonist – Famotidine 40mg OD (unless established on PPI)
- Bone protection as per NSSG Bone Protection protocol MM.3
    - Note patients will need dental review prior to any bisphosphonate treatment.

INTERACTIONS

Not exhaustive, for full details consult product literature/ reference texts

Carfilzomib is unlikely to be significantly affected by concomitant administration of medicines that act as 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).

Cases of QT prolongation, alongside cardiac toxicity have been reported with carfilzomib use. Evaluate necessity of any concurrent QT prolonging medicines against baseline ECG and level of risk, particularly if more than 3 agents involved long term.

EMETIC RISK

Low

EXTRAVASATION RISK:

Not a known vesicant.

No data is available regarding skin corrosion/irritation or extravasation.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

MHRA alert: Risk of reactivation of hepatitis B virus

Local guidelines can be consulted for prevention & management of reactivation. Note that the UK SACT Board has recently published a position statement on the subject which is strongly encouraged for local adoption.

Common adverse events:

Carfilzomib: Anaemia, neutropenia (inc. febrile neutropenia), thrombocytopenia, hypertension, cardiac toxicity, herpes zoster infection, fatigue, diarrhoea or constipation, nausea, anorexia,

dyspnea, cough, peripheral oedema, upper respiratory tract infection, pneumonia and electrolyte disturbances (hypo/hyperkalaemia, hypomagnesaemia, hyponatremia, hypo/hypercalcaemia), hyperglycaemia, hypoalbuminemia.

Dexamethasone: mood changes, restlessness, withdrawal effects, glucose intolerance, cushingoid appearance.

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Notable events:

- **Cardiac toxicity:** New or worsening cardiac failure (e.g., congestive cardiac failure, pulmonary oedema, decreased ejection fraction), myocardial ischaemia and infarction have occurred following administration. Fatal outcomes have been reported.
  Cases of QT interval prolongation have been reported in clinical studies and post-marketing data alongside cases of ventricular tachycardia.
  All patients should be monitored for evidence of volume overload, especially patients at higher risk for cardiac failure (e.g., >60yo) and all patients are mandated to receive baseline cardiac screening. **Withhold/stop treatment for any suspected cardiac event until recovery and consider whether to restart at 1 dose level reduction based on a benefit/risk assessment.**
- **Pulmonary Hypertension:** Withhold Carfilzomib and evaluate.
- **Dyspnoea**: Commonly reported, 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 kidney injury (AKI)**: 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 (ARDS), acute respiratory failure, and acute diffuse infiltrative pulmonary disease: Withhold Carfilzomib and evaluate promptly
- **Infusion reactions**: Symptoms may include 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. 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.

TREATMENT RELATED MORTALITY

< 5%

REFERENCES

1. Angen. Summary of Product Characteristics Kyprolis. Updated 31 Dec 2020.
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. Bringhen 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 frequency. Extravasation info. Dose modifications. Concurrent medication. Adverse events.	June 2018	1.1	June 2020
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
NSSG Myeloma Group	Annual protocol review 2021	June 2021	1.6	June 2022
NSSG Myeloma Group	Minor update	Dec 2021	1.7	June 2022
NSSG Myeloma Group	Minor formatting. Addition of tendonitis warning for levofloxacin. Addition of Apixaban 2.5mg BD	June 2023	2.0	June 2024

	embedded to aria as default thromboprophylaxis. Addition of Famotidine 40mg OD as stomach protection. Clarification to renal dose at treatment initiation. Re-wording throughout protocol without change of original intention.			

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.