Thames Valley
Strategic Clinical Network

CYCLOPHOSPHAMIDE / CARFILZOMIB / DEXAMETHASONE (CyCarDex)

INDICATIONS

Relapsed multiple myeloma.

This combination is not licensed in the UK and not funded by NHS England. Individual funding must be agreed prior to initiation. Prescribe in line with the individual Trust's governance and formulary framework.

TREATMENT INTENT

Disease modification

GENERAL PRE-ASSESSMENT

Ensure all the following staging investigations are done:

- FBC & film
- Clotting screen
- U&Es
- LFTs
- Calcium
- Uric acid
- CRP
- 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)
- Albumin & β_2 microglobulin for ISS staging
- 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)
- Group and save
- Imaging as per NICE/ network guidance and clinical presentation
- Bone marrow aspirate and trephine (with immunophenotyping for kappa/lambda if appropriate)

ADDITIONAL INVESTIGATIONS

- 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. Urine pregnancy test - before each course of chemotherapy in women aged 12 – 55 years of age unless they have been sterilised or undergone a hysterectomy.

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. Treatment must be agreed at the relevant MDT.

Wessex Regional Genetic Laboratory
Salisbury NHS Foundation Trust
Salisbury Disctrict Hospital
Salisbury
Wiltshire
SP2 8BJ

REGIMEN SPECIFIC PRE-ASSESSMENT

Evaluate for presence of cardiac issues. This is usually done by clinical assessment although ECHO and ECG may be useful in patients with previous cardiac history or over 70 years of age to document the extent of cardiac function prior to commencing therapy.

Baseline lying and standing blood pressure should be recorded prior to administration of cycle #1.

DRUG REGIMEN

Pre- and Post Hydration	Cycle 1 and cycle 2 day 1: pre- and post- hydration with 500mL sodium chloride 0.9% is recommended. Subsequent doses: pre- and post- hydration is recommended if lactate dehydrogenase (LDH) or uric acid is elevated and / or patients considered at risk for TLS. Encourage at least 1L oral fluids before and after each carfilzomib dose to maintain adequate hydration.	
Pre-medication	4 mg IV dexamethasone prior to carfilzomib dosing recommended for all doses in the first cycle, and prior to all subsequent doses if any carfilzomib related rigors, chills and / or dyspnoea occur.	
Carfilzomib	36 mg/m^2 intravenous infusion in 100mL glucose 5% over 30 minutes. For cycle 1 on Days 1 and 2 alone administer carfilzomib at 20mg/m^2 in 50mL glucose 5% over 10 minutes. Doses capped at BSA 2.2m^2	Days 1,2 8,9 and 15,16 Patient must be monitored for 1 hour following carfilzomib infusions during cycle 1 and cycle 2 day 1.

WITH		
Dexamethasone	40 mg po once a week Consider 20mg in elderly /frail patients	On days 1, 8, 15 & 22
WITH		
Cyclophosphamide	500 mg PO weekly	Days 1, 8 and 15

CYCLE FREQUENCY

Repeat every 28 days, continue until signs of disease progression or unacceptable toxicity. It is recommended that patients with a confirmed complete response receive 2 additional cycles of treatment beyond confirmation of this status to a maximum of 6 treatment cycles**.** Consider reduction of dexamethasone dose in elderly patients.

MAINTENANCE

Continue maintenance therapy for 18 months, provided no significant toxicity or disease progression.

Cycles 1-6 Maintenance

Carfilzomib	36 mg/m^2 intravenous infusion in 100mL glucose 5% over 30 minutes. Doses capped at BSA 2.2m^2	Days 1,2 and 15,16

Cycles 7-18 Maintenance

Carfilzomib	36 mg/m^2 intravenous infusion in 100mL glucose 5% over 30 minutes. Doses capped at BSA 2.2m^2	Days 1 and 2

DOSE MODIFICATIONS

Dose adjustments during treatment and re-initiation of treatment for combination therapy

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

Dose reduction guide for Carfilzomib

Current dose	Reduce dose to
36 mg/m^2	27 mg/m^2
27 mg/m^2	20 mg/m^2
20mg/m^2	15 mg/m^2

For carfilzomib doses 27mg/m^2, 20mg/m^2 and 15mg/m^2, administer in 50mL Glucose 5% over 10 minutes

Toxicity	Posology modification or delay
Haematological toxicity during a cycle	
• If Absolute neutrophil count < 0.5 x10^9 /L	Omit cyclophosphamide 1 week (continue dexamethasone). Restart at same dose when neutrophils and platelets recovered as above. If recurrent, i.e. if neutrophils < 1.0 x 10^9/L and platelets < 50 x 10^9/L on day 1 of subsequent cycles (when previously > than these levels), omit cyclophosphamide and consider dose reduction of cyclophosphamide for subsequent doses. If the patient was receiving 500 mg weekly, reduce to 400 mg, if 400 mg reduce to 300 mg, if 300 mg reduce to 200 mg. Withhold Carfilzomib dose, If recovered to ≥ 0.5 x10^9/L, continue at the same dose level. For subsequent drops to < 0.5 x10^9/L, follow the same recommendations as above and consider further dose level reduction when restarting Carfilzomib
• If platelet ≤ 10 x 10^9/L or evidence of bleeding with thrombocytopenia	Withhold Cyclophosphamide. Withhold Carfilzomib dose. if recovered to ≥ 10 x10^9/L and/or bleeding is controlled, continue at the same dose level For subsequent drops to < 10x10^9 /L, follow the same recommendations as above and consider 1 dose level reduction when restarting Carfilzomib.

Carfilzomib:

Renal	Hepatic
Serum creatinine ≥ 2 x baseline, or Creatinine clearance < 15 mL/min, or creatinine clearance decreases to ≤ 50% of baseline, or need for dialysis – **withhold Carfilzomib** Resume carfilzomib when renal function has recovered to within 25% of baseline; start at 1 dose level reduction.	Grade 3 liver toxicity; wait for toxicities to resolve to Grade 1 before further Carfilzomib dosing.

Cyclophosphamide:

Renal	Hepatic
Clinical decision GFR > 20mL/min 100% dose GFR 10 – 20mL/min 75% dose GFR < 10mL/min 50% dose	Exposure to active metabolites may not be increased, suggesting that dose reduction may not be necessary. Clinical decision.

INVESTIGATIONS (at the beginning of each cycle unless otherwise noted)

- 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.
- Random blood glucose/ blood sugar

CONCURRENT MEDICATIONS

Allopurinol 300 mg daily for 17 days for cycle 1 only (reduced dose if renal impairment).
Aciclovir 200 mg bd to tid for the duration of treatment and 3 months post therapy
Bone protection as per NSSG **Bone Protection** protocol MM3.
Fluconazole 50mg OD
Proton Pump Inhibitor H2 antagonist at clinician's discretion if needed.
Consider prophylactic co-trimoxazole, particularly in patients who have previously received an autograft.
Patients on oral hypoglycaemic may require close monitoring of blood sugar levels.

EMETIC RISK

Moderate emetic risk on cyclophosphamide days

ADVERSE EFFECTS/ REGIMEN SPECIFIC COMPLICATIONS

The most common adverse events occurring in at least 20% of patients treated with Carfilzomib in the combination therapy trial: decreased lymphocytes, anaemia, neutropenia, decreased total white blood cell count, decreased platelets, diarrhea, fatigue, thrombocytopenia, pyrexia, muscle spasm, cough, upper respiratory tract infection, decreased phosphate and hypokalemia.

- **Cardiac toxicities** include cardiac failure and myocardial infarction with fatal outcome, and myocardial ischemia. Withhold Carfilzomib and evaluate promptly.
- **Acute Renal Failure:** Monitor serum creatinine regularly
- **Tumor Lysis Syndrome (TLS):** Administer pre-treatment hydration. 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
- **Pulmonary Hypertension**: Withhold Carfilzomib and evaluate
- **Dyspnea:** For severe or life threatening dyspnea, 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.
- **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.
- **Embryo-fetal Toxicity:** Carfilzomib can cause fetal harm. Females of reproductive potential should avoid becoming pregnant while being treated.
- **Cyclophosphamide related toxicities include:** leucopenia, amenorrhoea, haematuria, hair loss, mucosal ulceration, anorexia, nausea and vomiting, pigmentation (typically affecting the palms and nails of the palms and the soles of the feet) pneumonitis and interstitial pulmonary fibrosis.
- **Dexamethasone related toxicities include:** mood changes, restlessness, withdrawal effects, glucose intolerance.

TREATMENT RELATED MORTALITY

< 5%

REFERENCES

1. Kyprolis prescribing information. http://pi.amgen.com/united_states/kyprolis/kyprolis_pi.pdf. Accessed 26th Oct 2015
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. Stewart AK, Rajkumar SV et al . Carfilzomib, Lenalidomide and dexamethasone for relapsed myeloma. N Engl J Med. 2015 Jan 8;372(2):142-52. doi: 10.1056/NEJMoa1411321. Epub 2014 Dec 6
5. Bringhen S et al. Carfilzomib, cyclophosphamide, and dexamethasone in patients with newly diagnosed multiple myeloma: a multicenter, phase 2 study. Blood. 2014 Jul 3;124(1):63-9. doi: 10.1182/blood-2014-03-563759. Epub 2014 May 22
6. Yong KL, et al. Carfilzomib, Cyclophosphamide and Dexamethasone Is Well Tolerated in Patients with Relapsed/Refractory Multiple Myeloma Who Have Received One Prior Regimen. Blood 2015;126: ASH Abstract 1840.
7. eMC UK Summary of Product Characteristics for KYPROLIS, Amgen, Dec 2016.

REVIEW

Name	Revision	Date	Version	Review date
Nadjoua Maouche, Pharmacist	Formatting, concurrent medication section removed, adverse effects revised	May 2016	1.2	May 2018
Faouzi Djebbari (Haematology Pharmacist)	Updated concurrent medication and references	July 2017	1.3	June 2019
Quality manager	Nursing care plan added	April 2021	1.4	June 2019

Nursing Care Plan
Cyclophosphamide Carfilzomib Dexamethasone

Indication: Relapsed Myeloma.
Frequency: 6 cycles of 28 days, then maintenance Carfilzomib until disease progression or unacceptable toxicity.
Alopecia: Possible hair thinning/loss due to cyclophosphamide.

CYCLOPHOSPHAMIDE: Alkylating agent.
Administered as orally on **days 1, 8, 15.**
Emetic risk: moderate.
Side effects: nausea/vomiting, diarrhoea, myelosupression, taste changes, minimal alopecia, bone marrow suppression, low risk haemorrhagic cystitis.

CARFILZOMIB: Proteasome inhibitor
Administered as an 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.
IV dexamethasone pre-med (4mg) for cycle 1 and all subsequent doses if a reaction with dyspnoea/rigor occurs.
Maintenance Carfilzomib is given on days 1, 2, 15, 16 on maintenance cycles 1-6 and on days 1, 2 on maintenance cycles 7-18.
Classification of extravasation: Not vesicant (There is 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 **days 1, 8, 15 and 22.** 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.
- 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.