Thames Valley
Strategic Clinical Network

CARFILZOMIB WITH POMALIDOMIDE AND DEXAMETHASONE

INDICATIONS

Relapsed or refractory multiple myeloma

This combination is unlicensed and not funded by NHS England. It is currently available for private patients only

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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)
   - β2 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

- 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

Additional Investigations

Plasma viscosity if hyperviscosity suspected.
If allogeneic transplant an option: Tissue typing of patient and siblings and CMV serology.
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.

Fertility - all patients should be offered fertility advice, as appropriate.

Hydration - fluid intake of at least 3 litres /day should be attempted.

Document patient's height and weight, dose on actual body weight.
Document patient's performance status.
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		**Cycle 1 (all carfilzomib days) and Cycle 2 Day 1**: pre- and post-hydration with 500ml sodium chloride 0.9% is recommended. **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. 4 mg IV dexamethasone prior to carfilzomib is 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*	**Cycle 1**	**Day 1 and 2** **20mg/m^2** IV infusion in 100 mL Glucose 5% over 30 minutes (max 44mg*)	Patient must be monitored for 1 hour following carfilzomib infusions during cycle 1 and on cycle 2 day 1.
		Day 8, 9, 15 and 16 **27mg/m^2** IV infusion in 100mL Glucose 5% over 30 minutes (max 123mg*)	
	Cycle 2 onwards	**Day 1, 2, 8, 9, 15 and 16** **27 mg/m^2** IV infusion in 100mL Glucose 5% over 30 minutes	
Dexamethasone		40mg if <75 years, OR 20mg if ≥75 years	Days 1,8,15,22
Pomalidomide		4mg PO daily on days 1-21	NOCTE

*Doses capped at BSA 2.2m^2

From cycle 7 onward, days 8,9 of carfilzomib could be dropped if patient achieves an excellent response.

CYCLE FREQUENCY

Repeat every 28 days for up to 18 cycles, unless signs of 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

Haematological toxicities:

Carfilzomib:

Carfilzomib dose reductions levels

Starting Dose	1st level dose reduction
27 mg/m^2	20 mg/m^2 *

* If toxicity does not resolve, discontinue treatment

Toxicity	Posology modification or delay
Haematological toxicity during a cycle	
• If Absolute neutrophil count < 0.5 x10^9 /L	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 1 dose level reduction to 20mg/m^2 when restarting carfilzomib
• If platelet ≤ 10 x 10^9/L or evidence of bleeding with thrombocytopenia	Withhold carfilzomib dose. If platelet recovers 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 to 20mg/m^2 when restarting carfilzomib

Pomalidomide:

Pomalidomide dose reduction levels

Dose level	Oral pomalidomide dose
Starting dose	4mg od
Dose level -1	3mg od
Dose level -2	3mg every other day

Toxicity	Dose Modification
Neutropenia:	
ANC < 0.5 x 10^9/L OR Febrile Neutropenia and ANC < 1.0 x 10^9/L. When ANC return to ≥1 x 10^9/l	Interrupt Pomalidomide, monitor FBC weekly Resume Pomalidomide at 3 mg OD
For each subsequent drop ANC < 0.5 x 10^9/L When ANC ≥ 1.0 x 10^9/L	Interrupt Pomalidomide Resume pomalidomide treatment at 3mg every other day (this is the lowest dose level)
Thrombocytopenia:	
Platelets < 25 x 10^9/L When Platelets ≥ 50 x 10^9/L	Interrupt Pomalidomide, monitor FBC weekly Resume pomalidomide treatment at 3mg every other day (this is the lowest dose level)
For each subsequent drop Platelets < 25 x 10^9/L When Platelets ≥ 50 x 10^9/L	Interrupt Pomalidomide Resume pomalidomide treatment at 3mg every other day (this is the lowest dose level)

If toxicities occur after dose reductions to 3 mg every other day, then discontinue Pomalidomide. Weekly injections of G-CSF can be administered to keep maintain dose intensity (aim to keep neutrophil counts >1.0)

Non-Haematological toxicities:

Carfilzomib:

• Non-haem toxicities should resolve to G1 or baseline before administering carfilzomib

Pomalidomide:

Toxicity	Dose Modification
-Grade 3 or 4 -When resolved to Grade ≤ 2	-Interrupt pomalidomide - Resume pomalidomide treatment at one dose level lower than the previous dose.
-Skin rash G2 or G3 -Skin rash G4 (exfoliative/bullous rash)	-Interrupt or discontinue pomalidomide -Discontinue pomalidomide
Angioedema (all grades)	Discontinue pomalidomide

Renal and Hepatic Impairment:

Carfilzomib:

Renal	Hepatic
Based on PK studies; No starting dose adjustment is recommended in patients with baseline mild, moderate, or severe renal impairment or patients on chronic dialysis. 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. For patients on dialysis receiving carfilzomib, the dose is to be administered after the dialysis procedure.	**Mild or moderate impairment**: Based on PK studies, no starting dose adjustment is 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. **Severe impairment**: The pharmacokinetics of carfilzomib has not been evaluated in patients with severe hepatic impairment.

Pomalidomide

Renal	Hepatic
No dose adjustment required in renal impairment On haemodialysis days, patients should take pomalidomide following haemodialysis	Avoid if serum bilirubin > 34 umol/L Careful monitoring is required in hepatic impairment

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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

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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 NSSG Bone Protection protocol MM.3
- Thromboprophylaxis/anticoagulation see VTE section below.

EMETIC RISK

Low

EXTRAVASATION RISK:

Carfilzomib is not known to be a vesicant. There are no data available regarding skin corrosion/irritation or extravasation. Follow institution's guideline on management of extravasation events in the event of carfilzomib extravasation.

MHRA alert (carfilzomib): 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

Carfilzomib:

- 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.
- Venous Thrombosis: Thromboprophylaxis is recommended.
- Infusion Reactions: 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.
- 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) and interstitial pulmonary fibrosis.
- Dexamethasone related toxicities include: mood changes, restlessness, withdrawal effects, glucose intolerance.

Pomalidomide:

- Venous thromboembolism (VTE): There is an increased risk of thrombosis with pomalidomide. Unless the patient is thought to be at particularly low-risk of thrombosis or high-risk of bleeding, some form of VTE prophylaxis is recommended as follows:

  1. Prophylactic low-molecular weight heparin OR
  2. Prophylactic DOAC e.g. apixaban 2.5mg bd (check product specific information)

  Aspirin can be appropriate for patients with no additional risk factors for thrombosis. It is generally not preferred for patients with additional risk factors.

  If VTE occurs, pomalidomide can be continued and the patient should be fully anticoagulated according to standard guidelines.

- Fatigue, dizziness and confusion
- Peripheral neuropathy, diarrhea/constipation, pneumonia, peripheral oedema.
- Risks of cardiac failure, interstitial lung disease and hepatotoxicity: There is a published MHRA drug alert (2015) on pomalidomide and risks of cardiac failure, interstitial lung disease and hepatotoxicity. See weblink: https://www.gov.uk/drug-safety-update/pomalidomide-imnovid-risks-of-cardiac-failure-interstitial-lung-disease-and-hepatotoxicity.

TREATMENT RELATED MORTALITY

< 5%

REFERENCES

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REVIEW

Name	Revision	Date	Version	Review date
Karthik Ramasamy (Lead Myeloma Clinician)	New Document	January 2020	1.0	June 2020