PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Carfilzomib, Lenalidomide and Dexamethasone Multiple Myeloma

PROTOCOL REF: MPHACLDMM
(Version No. 1.0)

Approved for use in:

- Patients who have relapsed multiple myeloma and who have received *one* previous line of therapy
- The previous line of therapy must have included bortezomib and the patient must have responded to bortezomib
- The patient must *not* have previously received lenalidomide unless lenalidomide was received as part of induction therapy prior to a stem cell transplant.
- Blueteq registration is required

Dosage:

Drug	Dose	Route	Frequency
Carfilzomib	**20 mg/m^2***	IV infusion	Day 1, 2, 8, 9, 15 & 16 of a 28 day cycle. *****Carfilzomib is administered at a starting dose of 20 mg/m^2 (maximum dose 44 mg) in cycle 1 on days 1 and 2. If tolerated, the dose should be increased on day 8 of cycle 1 to 27 mg/m^2 (maximum dose 60 mg). From cycle 13, the day 8 and 9 doses of carfilzomib are omitted.
Lenalidomide	**25mg**	Oral	Days 1 to 21 of a 28 day cycle
Dexamethasone	**40mg**	Oral	Days 1, 8,15 & 22 of a 28 day cycle *NB the dose can be reduced to 20mg if the patient is frail, >65 years old or at clinician discretion.*

Maximum number of cycles is 18 cycles of carfilzomib. A patient continuing to respond after completing 18 cycles of carfilzomib plus lenalidomide plus dexamethasone will continue on treatment with lenalidomide plus dexamethasone without carfilzomib.

Administration:

- Dexamethasone should be administered 30 minutes to 4 hours before carfilzomib.
- Adequate hydration is required before dose administration in cycle 1, especially in patients at high risk of tumour lysis syndrome or renal toxicity.
- Recommended hydration includes both oral fluids (30 mL/kg/day for 48 hours before day 1 of cycle 1) and intravenous fluids (250 mL to 500 mL of appropriate intravenous fluid before each dose in cycle 1). Give an additional 250 mL to 500 mL of intravenous fluids as needed following carfilzomib administration in cycle 1. Oral and/or intravenous hydration should be continued, as needed, in subsequent cycles.
- Lenalidomide capsules should be taken orally at about the same time on the scheduled days. The capsules should not be opened, broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food.
- If a dose of lenalidomide is missed and <12hours late the missed dose should be omitted and the next dose taken as scheduled
- Missed doses >12hours should be omitted and the next dose taken as scheduled
- If a patient vomits after taking a dose of lenalidomide, the patient should not repeat the dose and should resume dosing at the time of the next scheduled dose
- The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the pregnancy prevention programme (with lenalidomide) and provide patients with appropriate patient educational brochure and patient card.

Emetogenic risk:

Mildly emetogenic.

Supportive treatments:

- Allopurinol PO 300mg daily (cycle 1 only)
- Omeprazole PO 20mg daily
- Aciclovir PO 400mg twice daily
- Co-trimoxazole PO 480mg daily
- Anticoagulation – options include prophylactic dose of low molecular weight heparin (LWMH) (dalteparin 5000 units s/c OD) and treatment dose of LMWH in high risk

patients. For patients established on DOACs, patients may continue DOAC treatment or be switched to a LMWH.
- Metoclopramide PO 10mg TDS PRN
- Nystatin 1ml four times a day
- Chlorhexidine mouthwash 10ml twice a day

Extravasation risk:

Carfilzomib – non-vesicant

Interactions:

Carfilzomib

It is unknown whether carfilzomib is an inducer of CYP1A2, 2C8, 2C9, 2C19 and 2B6 at therapeutic concentrations. Caution should be observed when carfilzomib is combined with medicinal products that are substrates of these enzymes, such as oral contraceptives.

Caution should be observed when carfilzomib is combined with substrates of P-gp (e.g. digoxin, colchicine).

Lenalidomide

Agents that may increase the risk of thrombosis, such as HRT should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone

Monitoring of the digoxin concentration is advised during lenalidomide treatment.

There is an increased risk of rhabdomyolysis when statins are administered with lenalidomide, which may be simply additive. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of treatment.

For more detailed interactions please refer to the SPC (see references).

Treatment schedule:

Cycle 1

Day	Drug	Dose	Route	Diluent and rate
1 to 21	**Lenalidomide**	**25mg**	**PO**	Take in the evening

1	**Sodium chloride 0.9%**	**500ml**	**IV**	Over 60 mins
	Dexamethasone	**40mg****	**PO**	30 mins before chemotherapy
	Carfilzomib	**20mg/m^2**	**IV**	Glucose 5% 100mL over 10 minutes **Max dose 44mg.**
	Sodium chloride 0.9%	**500ml**	**IV**	Over 60 mins
2	**Sodium chloride 0.9%**	**500ml**	**IV**	Over 60 mins
	Carfilzomib	**20mg/m^2**	**IV**	Glucose 5% 100mL over 10 minutes **Max dose 44mg.**
	Sodium chloride 0.9%	**500ml**	**IV**	Over 60 mins
8	**Sodium chloride 0.9%**	**500ml**	**IV**	Over 60 mins
	Dexamethasone	**40mg**	**PO**	30 mins before chemotherapy
	Carfilzomib	**27mg/m^2**	**IV**	Glucose 5% 100mL over 10 minutes **Max dose 60mg.** **NB dose should only be increased if 20mg/m^2 dose was tolerated**
	Sodium chloride 0.9%	**500ml**	**IV**	Over 60 mins
9	**Sodium chloride 0.9%**	**500ml**	**IV**	Over 60 mins
	Carfilzomib	**27mg/m^2**	**IV**	Glucose 5% 100mL over 10 minutes **Max dose 60mg.**
	Sodium chloride 0.9%	**500ml**	**IV**	Over 60 mins
15	**Sodium chloride 0.9%**	**500ml**	**IV**	Over 60 mins
	Dexamethasone	**40mg**	**PO**	30 mins before chemotherapy
	Carfilzomib	**27mg/m^2**	**IV**	Glucose 5% 100mL over 10 minutes **Max dose 60mg.**
	Sodium chloride 0.9%	**500ml**	**IV**	Over 60 mins
16	**Sodium chloride 0.9%**	**500ml**	**IV**	Over 60 mins
	Carfilzomib	**27mg/m^2**	**IV**	Glucose 5% 100mL over 10 minutes **Max dose 60mg.**
	Sodium chloride 0.9%	**500ml**	**IV**	Over 60 mins
22	**Dexamethasone**	**40mg**	**PO**	

Cycle 2 to 12

Day	Drug	Dose	Route	Diluent and rate
1 to 21	**Lenalidomide**	**25mg**	**PO**	Take in the evening
1	**Dexamethasone**	**40mg**	**PO**	30 mins before chemotherapy
	Carfilzomib	**27mg/m^2**	**IV**	Glucose 5% 100mL over 10 minutes **Max dose 60mg.**
2	**Carfilzomib**	**27mg/m^2**	**IV**	Glucose 5% 100mL over 10 minutes **Max dose 60mg.**
8	**Dexamethasone**	**40mg**	**PO**	30 mins before chemotherapy
	Carfilzomib	**27mg/m^2**	**IV**	Glucose 5% 100mL over 10 minutes **Max dose 60mg.**
9	**Carfilzomib**	**27mg/m^2**	**IV**	Glucose 5% 100mL over 10 minutes **Max dose 60mg.**
15	**Dexamethasone**	**40mg**	**PO**	30 mins before chemotherapy
	Carfilzomib	**27mg/m^2**	**IV**	Glucose 5% 100mL over 10 minutes **Max dose 60mg.**
16	**Carfilzomib**	**27mg/m^2**	**IV**	Glucose 5% 100mL over 10 minutes **Max dose 60mg.**
22	**Dexamethasone**	**40mg**	**PO**	

Cycle 13 to 18

Day	Drug	Dose	Route	Diluent and rate
1 to 21	**Lenalidomide**	**25mg**	**PO**	Take in the evening
1	**Dexamethasone**	**40mg**	**PO**	30 mins before chemotherapy
	Carfilzomib	**27mg/m^2**	**IV**	Glucose 5% 100mL over 10 minutes **Max dose 60mg.**
2	**Carfilzomib**	**27mg/m^2**	**IV**	Glucose 5% 100mL over 10 minutes **Max dose 60mg.**
8	**Dexamethasone**	**40mg**	**PO**	

15	**Dexamethasone**	**40mg**	**PO**	30 mins before chemotherapy
	Carfilzomib	**27mg/m^2**	**IV**	Glucose 5% 100mL over 10 minutes **Max dose 60mg.**
16	**Carfilzomib**	**27mg/m^2**	**IV**	Glucose 5% 100mL over 10 minutes **Max dose 60mg.**
22	**Dexamethasone**	**40mg**	**PO**	

Cycle 19 onwards

Day	Drug	Dose	Route	Diluent and rate
1 to 21	**Lenalidomide**	**25mg**	**PO**	Take in the evening
1	**Dexamethasone**	**40mg**	**PO**	
8	**Dexamethasone**	**40mg**	**PO**	
15	**Dexamethasone**	**40mg**	**PO**	
22	**Dexamethasone**	**40mg**	**PO**	

***the dose of dexamethasone can be reduced to 20mg if the patient is frail, >65 years old or at clinician discretion.*

Main toxicities:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea, increased blood sugars, diabetes, VTEs, tumour lysis syndrome,

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Informed Consent	x				
Clinical Assessment by Dr/ANP	x		x		As clinically indicated or at the end of treatment
SACT Assessment (to include PS and toxicities)	x	x	x	x	Every cycle
Celgene Pregnancy Prevention Program Consent	x				
Celgene prescription authorization form		x	x	x	Every cycle
FBC	x	x	x	x	Every cycle
U&E & LFTs & Magnesium	x	x	x	x	Every Cycle
CrCl (Cockcroft and Gault)	x	x	x	x	Every cycle
Serum Igs/electrophoresis/serum free light chains (if indicated)	x	x	x	x	Every cycle
Hepatitis B virology screen	x				
Bone profile	x				
Blood glucose and HbA1c	x				Repeat as clinically indicated
Imaging as per clinical indication	x				
Dental assessment	x				
Pregnancy test	x	x	x	x	With every cycle for WCBP
ECG	x				If clinically indicated
Blood pressure	X	X	X	X	Can cause hypertensive crisis – measure once with each cycle
Weight recorded	x	x	x	x	Every cycle

Dose Modifications and Toxicity Management:

Haematological toxicity:

Carfilzomib

Haematologic toxicity	Recommended action
• Absolute neutrophil count < 0.5 × 10^9/L	• Stop dose - If recovered to ≥ 0.5× 10^9/L, continue at same dose level • For subsequent drops to < 0.5× 10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting carfilzomib
• Febrile neutropenia • Absolute neutrophil count < 0.5 × 10^9/L and an oral temperature > 38.5°C or two consecutive readings of > 38.0°C for 2 hours	• Stop dose • If absolute neutrophil count returns to baseline grade and fever resolves, resume at the same dose level
• Platelet count < 10 × 10^9/L or evidence of bleeding with thrombocytopenia	• Stop dose - If recovered to ≥ 10 × 10^9/L and/or bleeding is controlled continue at same dose level • For subsequent drops to < 10 × 10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting carfilzomib

Haematological toxicity:

Lenalidomide

Lenalidomide treatment must not be started if the ANC < 1.0 x 10^9/L, and/or platelet counts < 75 x 10^9/L or, dependent on bone marrow infiltration by plasma cells, platelet counts < 30 x 10^9/L.

Thrombocytopenia:

When platelets	Recommended course
Fall to < 30 x 10^9/L	Interrupt lenalidomide treatment

Return to ≥ 30 x 10^9/L	Resume lenalidomide at dose level 1
For each subsequent drop below 30 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 30 x 10^9/L	Resume lenalidomide at next lower dose level (dose level 2 or 3) once daily. Do not dose below 5mg once daily

Neutropenia:

When neutrophils	**Recommended course**
First fall to <0.5 x 10^9/L	Interrupt lenalidomide treatment***
Return to ≥ 0.5 x 10^9/L when neutropenia is the only observed toxicity	Resume lenalidomide at starting dose once daily
Return to ≥ 0.5 x 10^9/L when dose-dependent haematological toxicities other than neutropenia are observed	Resume lenalidomide at dose level 1 – once daily
For each subsequent drop below < 0.5 x 10^9/L	Interrupt lenalidomide treatment
Return to ≥ 0.5 x 10^9/L	Resume lenalidomide at next lower dose level (dose level 2, 3 or 3) once daily. Do not dose below 5mg once daily.

***At the physician's discretion, if neutropenia is the only toxicity at any dose level, add granulocyte colony stimulating factor (G-CSF) and maintain the dose level of lenalidomide.

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

Dosing in renal and hepatic impairment:

Renal	Carfilzomib	• No ***starting*** dose adjustment for carfilzomib is recommended in patients with baseline mild, moderate, or severe renal impairment or patients on chronic dialysis based on available pharmacokinetic data.

<table>
<tr><td rowspan="2"></td><td></td><td>For patients on dialysis receiving Kyprolis, the dose is to be administered after the dialysis procedure
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.
If during treatment the serum Cr increases ≥ 2 times baseline OR CrCl decreases to < 15ml/min OR CrCl decreases to ≤ 50% of baseline then carfilzomib should be withheld and restarted when renal function has recovered to with 25% of baseline; consider resuming at 1 dose level reduction.</td></tr>
<tr><td>Lenalidomide</td><td>No dose adjustments are required for patients with mild renal impairment and multiple myeloma. The following dose adjustments are recommended at the start of therapy and throughout treatment for patients with moderate or severe impairment renal function or end stage renal disease.

<table><tr><th>Renal function (CrCl – mL/min)</th><th>Dose adjustment</th></tr><tr><td>Moderate (30 ≤ CrCl < 50)</td><td>10mg ONCE daily *</td></tr><tr><td>Severe (<30, not requiring dialysis)</td><td>15mg EVERY OTHER day</td></tr><tr><td>End Stage Renal Disease (<30)</td><td>5mg ONCE daily. On dialysis days, the dose should be administered following dialysis.</td></tr></table>
*The dose may be escalated to 15mg once daily after 2 cycles if the patient is not responding to treatment and is tolerating the treatment</td></tr>
<tr><td>Hepatic</td><td>Carfilzomib</td><td>No starting dose reduction for mild or moderate liver function is required. No information on starting doses in patients with severe liver disease is available because carfilzomib was not studied in this patient population. NB greater levels of adverse effects were</td></tr>
</table>

		seen in patients with mild and moderate baseline hepatic impairment. • If ***during*** treatment bilirubin increases > 63micromol/L or ALT > 165 (women) or > 205 (men) then carfilzomib should be withheld until results have resolved or returned to baseline; consider resuming at 1 dose level reduction.
	Lenalidomide	Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations

All other grade 3 and 4 toxicities	Carfilzomib	• Stop until resolved or returned to baseline • Consider restarting the next scheduled treatment at 1 dose level reduction
	Lenalidomide	Treatment should be stopped and only restarted at next lower dose level when toxicity has resolved to ≤ Grade 2 depending on the physician's discretion

Dose level reductions for carfilzomib	**Carfilzomib Dose**	**First carfilzomib dose reduction**	**Second carfilzomib dose reduction**	**Third carfilzomib dose reduction**
	27 mg/m^2	20 mg/m^2	15 mg/m^2	Discontinue

Dose level reductions for lenalidomide	
Starting dose	25mg
Dose level 1	15mg
Dose level 2	10mg
Dose level 3	5mg

References:

1. Summary of Product Characteristics, Revlimid®, Lenalidomide, Celgene, last updated 16th Sep 2019 [accessed on 5/11/21] https://www.medicines.org.uk/emc
2. Summary of Product Characteristics, Kyprolis, Amgen last updated 08/21 accessed on 5/11/21] https://www.medicines.org.uk/emc

Circulation/Dissemination

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Version History

Date	Version	Author name and designation	Summary of main changes
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