SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

LENALIDOMIDE, CYCLOPHOSPHAMIDE & DEXAMETHASONE MULTIPLE MYELOMA

PROTOCOL REF: MPHALCDMM
(Version No. 1.0)

Approved for use in:

- Patients who have received two or more lines of prior therapies for multiple myeloma (cyclophosphamide must not be added to 1st line or 2nd line treatment with lenalidomide and dexamethasone). Triple therapy must be prescribed from cycle 1.

  Patients must have:
  - ECOG PS 0-2
  - No previous treatment with lenalidomide
  - Not be eligible for a stem cell transplantation
  - If cyclophosphamide is used in combination with lenalidomide and dexamethasone, the cyclophosphamide must be initiated with the first cycle of lenalidomide plus dexamethasone and not as a result of disease progression whilst on lenalidomide and dexamethasone.

Blueteq registration required: see blueteq for further eligibility criteria

Dosage:

Drug	Dose	Route	Frequency
Cycles 1-4			
Lenalidomide	**25mg ONCE daily**	PO	Days 1-21
Cyclophosphamide	**500mg**	PO	Days 1 & 8 (weekly) *(can be added to day 15 at clinician discretion)*
	or		

	50mg	PO	Once daily on days 1 to 21
Dexamethasone	**40mg ONCE daily***	PO	Days 1-4, 9-12 and 17-20
Cycles 5 onwards			
Lenalidomide	**25mg ONCE daily**	PO	Days 1-21
Cyclophosphamide	**500mg**	PO	Days 1 & 8 (weekly)
	or		
	50mg	PO	Once daily on days 1 to 21
Dexamethasone	**40mg ONCE daily***	PO	Days 1-4

*Differing doses and frequencies of dexamethasone may be used at the discretion of the prescriber. Prescribers should carefully evaluate which dose of dexamethasone to use, considering the condition and disease status of the patient.

Cycle every 28 days – treatment to be continued until disease progression or intolerance

Administration +/- Counselling Points:

- 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 dose is missed and <12hours late the missed dose should be taken. Missed doses >12hours should be omitted and the next dose taken as scheduled.
- Dexamethasone tablets should be taken in the morning after food.
- 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 and provide patients with appropriate patient educational brochure and patient card.
- Cyclophosphamide should be taken on an empty stomach; that is an hour before food or two hours after food.

Emetogenic risk:

Low risk

Supportive treatments:

- Allopurinol 300mg daily for 28 days (cycle one only)
- Aciclovir 400mg twice daily for the duration of treatment
- Co-trimoxazole 480mg daily for the duration of treatment
- Omeprazole 20mg daily - review each cycle
- Ondansetron 4-8mg TDS PRN for 5-7 days, usually prescribed for cycle 1 only
- Nystatin 1mL QDS **OR** Fluconazole 50mg daily for antifungal prophylaxis (if higher doses of steroids being used, review each cycle)
- VTE prophylaxis:
    - Dalteparin 5,000 units subcutaneous injection daily (or alternative prophylactic LMWH)
    - Therapeutic dose LMWH in high risk patients. Patients may continue previously established DOAC treatment or be switched to a LMWH.
    - Aspirin 75mg daily (for those patients who decline LMWHs or for those deemed to be low risk on long term treatment)
- Consider adding Clarithromycin 500mg BD if poor response to initial treatment to augment effect of lenalidomide. Be mindful of drug-drug interactions. Dose can be reduced to 250mg BD if tolerability an issue. Avoid in patients with a history of C. Difficile.

Dosing in renal and hepatic impairment:

	Lenalidomide	**Creatinine Clearance (mL/min)**	**Dose Adjustment**
		30 - 50	10mg ONCE daily*
		<30 not requiring dialysis	15mg EVERY OTHER day
		End stage renal disease (<30)	5mg ONCE daily. On dialysis, the dose should be administered after dialysis
		*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	
	Cyclophosphamide	**Creatinine clearance (mL/min)**	**Dose Adjustment**

		10 - 20	75% dose
		<10	Not recommended. If unavoidable consider 50% dose

Hepatic	**Lenalidomide**	Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations.
	Cyclophosphamide	Exposure to active metabolites may not be increased, suggesting that dose reduction may not be necessary. Clinical decision.

Interactions:

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.
- **Digoxin** – concomitant administration with lenalidomide increased plasma exposure of digoxin, monitoring of the digoxin concentration is advised during lenalidomide treatment.
- **Statins** – there is an increased risk of rhabdomyolysis when statins are administered with lenalidomide. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of treatment.

Dexamethasone:

- Dexamethasone is a moderate inducer of CYP3A4. Co-administration of dexamethasone with other drugs that are metabolised by CYP3A4 (e.g. indinavir, erythromycin) may increase their clearance, resulting in decreased plasma concentrations.
- Concomitant treatment with CYP3A4 inhibitors may increase the risk of systemic side effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side effects in which case patients should be monitored for systemic corticosteroid side effects.

Cyclophosphamide

- Substances that reduce the efficacy (via reduced activation) of cyclophosphamide include: aprepitant, bupropion, busulfan, ciprofloxacin, chloramphenicol, fluconazole itraconazole, clopidogrel, sulphonamides and thiotepa.
- An increased risk of side-effects may occur (via increased concentration of cytotoxic metabolites) with allopurinol, chloral hydrate, cimetidine, disulfiram, glyceraldehyde, CYP450 inducers (rifampicin, phenobarbital, carbamazepine, phenytoin, St John's Wort).
- An increased risk of hepatotoxicity (liver necrosis) with azathioprine

Please refer to the relevant SPC for more drug-drug interaction information.

Main toxicities:

Infections, thrombocytopenia, neutropenia, anaemia, venous thromboembolism (VTE), secondary MDS, peripheral neuropathy, hypokalaemia, rash, headache, diarrhoea, constipation, abdominal pain, nausea, vomiting, fatigue, muscle spasm, abnormal LFTs.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Informed Consent	X				
Clinical & SACT Assessment	X	X	X	X	Prior to every cycle
Pregnancy Prevention Program (PPP) Consent	X				
Prescription authorization form		X	X	X	With ~~to~~ every prescription for lenalidomide
FBC	X	X	X	X	Weekly for the first month and then monthly thereafter unless clinically indicated. Prior to every cycle.
U&E & LFTs	X	X	X	X	Prior to every cycle
CrCl (Cockcroft and Gault)	X	X	X	X	Prior to every cycle
Bone profile	X				As clinically indicated
Virology screen (Hep B, C, HIV)	X				
Serum Igs/electrophoresis/serum free light chains (if indicated)	X	X	X	X	Prior to every cycle
Neurological assessment (for neuropathy)	X	X	X	X	Prior to every cycle
Height	X				
Weight	X	X	X	X	Prior to every cycle
Dental assessment	X				As clinically indicated
HbA1C	X				As clinically indicated
Respiratory Rate					If clinically indicated
PS recorded	X	X	X	X	Prior to every cycle
Blood glucose	X				Repeat if clinically indicated
Pregnancy test	X				If clinically indicated as part of PPP
Thyroid function test	X				If clinically indicated

Dose Modifications and Toxicity Management:

Haematological toxicity:

Cycle one can proceed if-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 75 x 10^9/L

Subsequent cycles can proceed if-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 50 x 10^9/L (or >30 x 10^9/L as below)

Note therapy can proceed if values are below these levels if cytopenias known to be secondary to disease.

Please note that cyclophosphamide should be reduced or omitted in preference to reducing the dose of lenalidomide to manage haematological toxicity.

Cyclophosphamide			
Neutrophils	**And/or**	**Platelets**	**Dose Modification**
<1.0 x10^9/L	or	<50 x10^9/L	Delay cyclophosphamide until recovery and restart at same dose. If recurrent cytopenia then consider dose reduction of cyclophosphamide. Consider GCSF if appropriate.

Dose step reductions:

Dose Level	Lenalidomide Dose
Starting dose	25mg
Dose level 1	15mg
Dose level 2	10mg
Dose level 3	5mg

Lenalidomide			
Neutrophils (x10^9/L)	**And /or**	**Platelets (x10^9/L)**	**Recommendation**
First fall to <0.5	or	Fall to < 30	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	and	Return to ≥ 30	Resume lenalidomide at dose level 1 – once daily
Subsequent drop below < 0.5	or	Subsequent drop < 30	Interrupt lenalidomide treatment
Return to ≥ 0.5	and	Return to ≥ 30	Resume lenalidomide at next lower dose level (dose level 2, 3 or 3) once daily. Do not dose below 5mg once daily.

Non- Haematological toxicity:

For other grade 3 or 4 toxicities judged to be related to 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.

Lenalidomide interruption or discontinuation should be considered for grade 2 or 3 skin rash. Lenalidomide must be discontinued for angioedema, grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected and should not be resumed following discontinuation from these reactions.

References:

1. Summary of Product Characteristics, Cyclophosphamide 50mg tablets, Baxter Healthcare Ltd, last updated 14th Dec 2016 [accessed 28th Jan 2023] https://www.medicines.org.uk/emc/product/1813/smpc
2. Summary of Product Characteristics, Lenalidomide, Zentiva, last updated July 2022 [accessed on 28th Jan 2023] https://www.medicines.org.uk/emc/product/13871/smpc

3. Summary of Product Characteristics, Dexamethasone tablet 2mg, Aspen, last updated 14th Aug 2022 [accessed on 28th Jan 2023] https://www.medicines.org.uk/emc/product/5411/smpc#gref
4. NICE TA171 – Lenalidomide for the treatment of multiple myeloma in people who have received at least two prior therapies. Published: 18 June 2009 www.nice.org.uk [accessed on 28th Jan 2023]
5. Blueteq Form reference: LEN3. https://www.england.nhs.uk/wp-content/uploads/2017/04/national-cdf-list-v1.249.pdf [accessed 28th Jan 2023]

Circulation/Dissemination

Date added into Q-Pulse	9th June 2023
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
April 2023	1.0	**Jade Marsh / Jennifer Gibson**	New protocol