Systemic Anti Cancer Therapy Protocol

CTDa – Cyclophosphamide, Thalidomide & Dexamethasone (attenuated) Multiple Myeloma

PROTOCOL REF: MPHACDTAHA
(Version No: 1.0)

Approved for use in:

- Thalidomide in combination with cyclophosphamide and a corticosteroid is recommended as an option for the treatment of multiple myeloma in people for whom high-dose chemotherapy with stem cell transplantation is considered inappropriate
- EGOG PS 0-2
- The Celgene Pregnancy Prevention Program must be observed for all male and female patients. Prescribing and dispensing of thalidomide must be in line with the pregnancy prevention program.
- This is the *attenuated CTD* protocol which is suitable for frailer patients. Please ensure you have the *correct protocol* before proceeding.
- **Blueteq registration is not required**

Dosage:

Drug	Dose	Route	Frequency
Cyclophosphamide	**500mg**	Oral	Day 1, 8, 15 and 22
Thalidomide	**50mg once daily at night. Titrate up to max daily dose of 200mg nocte**	Oral	Days 1 to 28 (continuous)
Dexamethasone	**20mg**	Oral	Days 1 to 4 and days 15 to 18

Maximum of 9 cycles (28 day cycle)

Administration and Counselling Points:

- Anticoagulation is required throughout treatment due to thrombotic effect of thalidomide.
- Cyclophosphamide should be taken on an empty stomach; that is an hour before food or two hours after food.
- 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.

Anti-emetic risk:

Moderately emetogenic.

Supportive treatments:

- Allopurinol 300mg daily (cycle 1 only)
- Ondansetron 4mg three times a day when required (review need after cycle 1)
- Aciclovir PO 400mg twice a day
- Co-trimoxazole PO 480mg daily
- Nystatin 1ml QDS or fluconazole PO 50mg od (higher risk patients only)
- Omeprazole 20mg daily
- Anticoagulation – options include prophylactic dose of low molecular weight heparin (LWMH), treatment dose of LMWH in high risk patients. For patients established on. DOACs, patients may continue DOAC treatment or be switched to a LMWH.

Interactions:

Thalidomide

Thalidomide has sedative properties, thus may enhance the sedation induced by anxiolytics, hypnotics, antipsychotics, H_1antihistamines, opiate derivatives, barbiturates and alcohol. Caution should be used when thalidomide is given in combination with medicinal products that cause drowsiness.

Due to thalidomide's potential to induce bradycardia, caution should be exercised with medicinal products having the same pharmacodynamic effect such as active substances known to induce torsade de pointes, beta blockers or anticholinesterase agents.
Medicinal products known to be associated with peripheral neuropathy (e.g. vincristine and bortezomib) should be used with caution in patients receiving thalidomide.

Cyclophosphamide

Substances that reduce the efficacy of cyclophosphamide include:
aprepitant, bupropion, busulfan, ciprofloxacin, chloramphenicol, azole-antimycotics (e.g. fluconazole and itraconazole, CYP2B6 and CYP3A4 inhibitors (e.g. nevirapin and ritonavir): co-administration may reduce the efficacy of cyclophosphamide, prasugrel, sulphonamides, e.g. sulfadiazine, sulfamethoxazole and sulfapyridine, thiotepa, grapefruit (fruit or juice), rifampicin, St. John's wort.

An increased risk of side-effects may occur with:
Azathioprine: increased risk of hepatotoxicity (liver necrosis), chloral hydrate, cimetidine, disulfiram, glyceraldehyde, protease inhibitors, saquinavir, rifampin, phenobarbital, carbamazepine, phenytoin, St. John's wort, benzodiazepines, corticosteroids and dabrafenib.

There is an increased risk of cardiotoxicity when cyclophosphamide is co-administered with: Anthracyclines, mitomycin, cytarabine, pentostatin and radiation therapy.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Dexamethasone**	**20mg**	**PO**	In the morning with food
	Cyclophosphamide	**500mg**	**PO**	
2 to 4	**Dexamethasone**	**20mg**	**PO**	In the morning with food
8	**Cyclophosphamide**	**500mg**	**PO**	
15	**Dexamethasone**	**20mg**	**PO**	In the morning with food
	Cyclophosphamide	**500mg**	**PO**	
16 to18	**Dexamethasone**	**20mg**	**PO**	In the morning with food

22	**Cyclophosphamide**	**500mg**	**PO**	
1 to 28	**Thalidomide**	**50 to 200mg**	**PO**	Nocte

Main toxicities:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea, peripheral neuropathy, drowsiness and venous thromboembolism.

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3+	Ongoing
Informed consent	X				
Clinical Assessment	X	X	X	X	
SACT Assessment (including performance status and toxicity assessment		X	X	X	
Celgene Pregnancy Prevention Program Consent	X				
Celgene prescription authorization form		X	X	X	
Serum Igs/electrophoresis/serum free light chains (if indicated)	X	X	X	X	
FBC	X	X	X	X	
U&E & LFTs & Calcium profile	X	X	X	X	
CrCl (Cockcroft and Gault)	X				
Blood pressure measurement	X				Repeat if clinically indicated
Screen for Hep B/ C and HIV	X				
Dental assessment	X				
HbA1C and blood glucose	X				Repeat as clinically indicated
Imaging as per NICE/network guidance and clinical indication	X				Repeat as clinically indicated
Height	X				
Weight	X	X	X	X	Every cycle
Pregnancy test	X				If clinically indicated – must be repeated every cycle in women of childbearing potential

Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 50 x 10^9/L

If neutrophil <1 x 10^9/l or platelets <50 x 10^9/l and it thought to be treatment related:

- Omit cyclophosphamide for 1 to 3 weeks and reduce dose (e.g. to 400mg or 300mg)
- Add G-CSF for 2 to 3 days per cycle or week

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.

Dosing in renal and hepatic impairment:

Thalidomide
Thalidomide has not formally been studied in patients with impaired renal or hepatic function. No specific dose recommendations for these patient populations are available. Patients with severe organ impairment should be carefully monitored for adverse reactions.

Cyclophosphamide	
Renal	
CrCl (ml/min)	Dose
10-29	Consider 75% of dose
<10 or haemodialysis	Not recommended. If unavoidable consider 50% of dose.
Liver	
Severe liver dysfunction	Not recommended

Peripheral Neuropathy

Severity of neuropathy	**Modification of dose and regimen**
Grade 1 (paraesthesia, weakness and/or loss of reflexes) with no loss of function	Continue to monitor the patient with clinical examination. Consider reducing dose if symptoms worsen. However, dose reduction is not necessarily followed by improvement of symptoms.
Grade 2 (interfering with function but not with	Reduce dose or interrupt treatment and

activities of daily living)	continue to monitor the patient with clinical and neurological examination. If no improvement or continued worsening of the neuropathy, discontinue treatment. If the neuropathy resolves to Grade 1 or better, the treatment may be restarted, if the benefit/risk is favourable.
Grade 3 (interfering with activities of daily living)	Discontinue treatment
Grade 4 (neuropathy which is disabling)	Discontinue treatment

References:

1. https://www.medicines.org.uk/emc cyclophoshamide (accessed March 2020)
2. https://www.medicines.org.uk/emc thalidomide (accessed March 2020)
3. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol* 2019;**20:** e201–08
4. Cheshire and Merseyside Strategic Clinical Network CTDa Protocol