THALIDOMIDE & DEXAMETHASONE +/- CYCLOPHOSPHAMIDE (CTD / CTDa)

First or subsequent-line chemotherapy for multiple myeloma or AL amyloidosis
The attenuated version, CTDa, to be used in selected elderly patients

Drugs/Dosage:

Thalidomide initial dose 50mg po daily, titrating upwards every 2 weeks to a maximum of 200mg daily, depending on tolerability

Dexamethasone 40mg (CTD) or 20mg (CTDa) po once daily in the morning on Days 1 to 4 and Days 15 to 18* (4-day "pulses")

*after 3 cycles, reduce dexamethasone to Days 1 to 4 only

or, an alternative for CTDa where pulsed dex is not tolerated, or not suitable:
Dexamethasone 20 – 40**mg po once weekly[1] on Days 1, 8, 15 & 22

** Dexamethasone dose may be chosen according to age of patient, disease burden and prior tolerability

+/- (do not include in patients with cytopenias):
Cyclophosphamide 500mg po once weekly on Days 1, 8, 15 and 22

Administration:

Cyclophosphamide available as 50mg tablets, to be swallowed whole with a full glass of water
Thalidomide is available as 50mg capsules. The daily dose should be taken at bedtime to avoid problems with day-time sedation. Patients should be advised not to drive or operate machinery for 8 hours after each dose.
Dexamethasone to be taken in the morning with or after food

Other drugs:

Allopurinol (dose according to renal function) – review after 4 weeks
Fluconazole 50 – 150mg po od for antifungal prophylaxis
Use of proton pump inhibitor or H_2 receptor antagonist is recommended whilst treating with steroids
Consider PCP prophylaxis – prescribe according to unit practice/protocol
Laxative as required for thalidomide-induced constipation
Thromboprophylaxis, according to unit practice, is recommended in the absence of specific contraindication

Frequency:

4 weekly cycle
Treat for a minimum of 4 cycles until paraprotein / serum free light chain stable for 3 months. It is unusual to require more than 6 cycles of treatment.

Main Toxicities:

myelosuppression; haemorrhagic cystitis; teratogenicity (see Comments); sedation (take thalidomide at bedtime); dry skin or rash; peripheral neuropathy; dizziness; bradycardia and syncope; constipation (often requiring laxatives); alopecia (mild); increased risk of thromboembolic events; steroid side effects

Reason for Update: advice for cyclophosphamide in renal impairment updated, for consistency with other cyclophos-containing protocols; adapted to allow +/- cyclophos and so separate Thal-dex protocol not needed	Approved by Chair of Alliance TSSG: Dr A Laurie
Version: 6	Date: 12.12.14
Supersedes: Version 5	Review Date: January 2017
Prepared by: S Taylor	Checked by: C Tucker

Anti- emetics:	Days 1, 8, 15 and 22 - moderately emetogenic (N.B. Due to high dose dexamethasone, anti-emetic doses of dexamethasone are not required) Remainder of cycle – mildly emetogenic	
Regular Investigations:	FBC	at least every 4 weeks, more frequently if indicated
	U&Es & LFTs	every 4 weeks
	Serum & urine electrophoresis for para-protein quantification and Bence Jones protein	every 4 weeks
	Pregnancy test	every 4 weeks for women of child bearing potential
	Blood glucose monitoring	see Comments
	Blood pressure monitoring	see Comments

Comments: Blood glucose and blood pressure monitoring to be tailored according to individual patient needs.

Thalidomide is highly teratogenic:

- women of child bearing potential must have a negative pregnancy test within 3 days prior to starting treatment. Pregnancy testing should be repeated monthly thereafter until one month after stopping thalidomide (or every 2 weeks in women with irregular menstrual cycles). If a woman taking thalidomide thinks she may be pregnant she must stop the drug immediately.
- men taking thalidomide must use a barrier method of contraception throughout treatment and for one week after stopping, if their partner is capable of bearing children.
- women of child-bearing potential must use one agreed effective method of contraception for at least 4 weeks before starting thalidomide, while on thalidomide and for one month after. (The combined oral contraceptive pill is not recommended due to the increased risk of thromboembolism)

Thalidomide is supplied through the Celgene Pregnancy Prevention Programme. All aspects of the programme should be followed, including completion of an authorisation form by both doctor and pharmacist with every cycle.

Dose Modifications

Haematological Toxicity:

Cycle 1: No dose modifications

Subsequent cycles: If neutrophil count < 1.0 x 10^9/L or platelets < 50 x 10^9/L, continue with dexamethasone and thalidomide. Omit 1 – 3 weeks of cyclophosphamide, then re-introduce cyclophosphamide, with consideration to using a reduced dose.

If low counts are thought to be due to marrow infiltration, discuss with Consultant.

Renal Impairment:

CrCl (ml/min)	Cyclophosphamide Dose
> 20	Give 100% dose
10 – 20	Omit cyclophosphamide until renal function improved, or give 75% dose
< 10	Omit cyclophosphamide until renal function improved, or give 50% dose

Thalidomide Side Effects:	Mild neuropathy is very common and, in the absence of progression of the neuropathy, the thalidomide dose may be kept the same. If the symptoms begin to worsen, consider a dose reduction of up to 50%. For Grade 2 neuropathy, a dose reduction of up to 50%, or a break in treatment, is required. If neuropathy does not improve, discontinue thalidomide permanently. If neuropathy resolves to Grade 1 or better, continue with the 50% dose if risk/benefit favourable. In more severe cases (Grade 3 – 4), it is recommended that thalidomide should be permanently discontinued. However, if symptoms do resolve, re-introducing thalidomide at a lower dose may be considered. However, neuropathy is often not reversible.
Steroid Side Effects:	If severe steroid-related side effects develop, dose reduction to dexamethasone 20mg per dose may be considered, or omit one "pulse" of dexamethasone, according to individual case.
Patient Information:	Celgene Pregnancy Prevention Programme Booklet Macmillan leaflet for CTD "Thalidomide and Myeloma" Infoguide, and AL Amyloidosis Essential Guides, produced by Myeloma UK, are also recommended (available at www.myelomaonline.org.uk)
References:	MRC Myeloma IX trial (2004) Doses and scheduling as NLCN Guidelines for Treatment of Myeloma, Oct 2009