Cyclophosphamide, Thalidomide and Dexamethasone (CTD and CTDa)

Indication

First line treatment of multiple myeloma in patients for whom other treatments are contraindicated.

Treatment of relapsed multiple myeloma.

ICD-10 codes

Codes with a pre-fix C90

Regimen details

CTD

Day	Drug	Dose	Route
1, 8, 15	Cyclophosphamide	500mg	PO
1-21 (continuously)	Thalidomide	50mg ON*	PO
1-4 and 12-15	Dexamethasone	40mg OM**	PO

* Thalidomide may be increased to 100mg ON during cycle 1 if tolerated and to 200mg ON for subsequent cycles.
**Dexamethasone dose may be reduced based on tolerability.

An attenuated version of this protocol may be given on a 28 day cycle if renal impairment or intolerance to full doses:

CTDa

Day	Drug	Dose	Route
1, 8, 15 and 22 Or 1-28 (continuously)	Cyclophosphamide	500mg weekly Or 50mg daily	PO
1-28 (continuously)	Thalidomide	50mg ON	PO
1-4 and 15-18	Dexamethasone	20mg OM	PO

Cycle frequency

21 days for CTD or 28 days for CTDa.

Number of cycles

Treat to maximum response and according to tolerability. Minimum of 4 cycles and usually 6-8.

Administration

Cyclophosphamide is available as 50mg tablets. Tablets should be swallowed whole with a full glass of water.

Thalidomide is available as 50mg capsules. The dose should be taken at night time as thalidomide may cause sedation.

Women of child bearing potential must have a **NEGATIVE PREGNANCY TEST** within 72 hours before starting thalidomide therapy, and then before each cycle during treatment until one month after stopping treatment (every 2 weeks if irregular periods). Women of child bearing potential and males must use adequate contraception. If a woman thinks she may be pregnant she must stop taking thalidomide immediately. See Thalidomide Celgene Pregnancy Prevention Programme.

Dexamethasone is available as 500microgram and 2mg tablets. The dose should be taken in the morning, with or after food.

Pre-medication

Nil

Emetogenicity

This regimen has low emetogenic potential.

Additional supportive medication

H_2 antagonist or proton pump inhibitor
Allopurinol 300mg OD (100mg OD if CrCl< 20mL/min) for patients with a high tumour burden, for the first cycle only.
Bisphosphonates as per local policy
Antifungal, antiviral and PCP prophylaxis as per local policy
Thromoboprophylaxis is required – risk assess patient and consider prophylactic LMWH as per local policy (unless platelet count < 30 x 10^9/L, then withhold until recovered). If patient is already taking warfarin consider switch to treatment dose LMWH or DOAC (as applicable within NICE guidance).

Extravasation

N/A

Investigations – pre first cycle

Investigation	Validity period
FBC and film	7 days
U+Es (including creatinine)	7 days
LFTs	7 days
Calcium	7 days
Glucose	7 days
Pregnancy test (female of child bearing potential)	3 days

Serum electrophoresis (or alternative biological measure of response if M protein not measurable)
Bone marrow aspirate and trephine, including FISH
Assessment of venous thromboembolic risk

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	96 hours
U+Es (including creatinine)	7 days
LFTs	7 days
Calcium	As clinically indicated
Glucose	As clinically indicated
Pregnancy test (if applicable)	3 days

Serum electrophoresis (or alternative biological measure of response if M protein not measurable). For non-secretory disease consider bone marrow assessment after 4 cycles. Monitoring calcium levels and as indicated glucose.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 70 x 10^9/L
Creatinine clearance	> 20mL/min
Bilirubin	< 1.5 x ULN

Dose modifications

- **Haematological toxicity**

Treatment on day 1 should only be initiated if neutrophils ≥ 1.0 x 10^9/L and platelets ≥ 70 x 10^9/L.

If cytopenia considered to be disease related, treatment may be given at consultant discretion.

- **Renal impairment**

Cyclophosphamide:

CrCl (mL/min)	**Cyclophosphamide dose***
> 20	100%
10-20	75%
< 10	50%

*CTDa with 50mg cyclophosphamide daily does not usually require further dose adjustment.

- **Hepatic impairment**

Cyclophosphamide:

Hepatic impairment has been associated with a decreased activation of cyclophosphamide. This should be considered as it may alter the effectiveness of treatment.

- **Other toxicities**

Thalidomide

Toxicity	**Definition**	**Thalidomide dose**
Peripheral neuropathy	Grade 1-2	Reduce thalidomide dose by 50% and consider discontinuing.
	Grade 3-4	Stop thalidomide (usually permanently). If symptoms resolve consider starting at 50mg for subsequent cycles (dose may be escalated in 50mg increments)
Sedation, constipation, rash, fatigue, tremor, oedema	Grade 3-4	Stop thalidomide for remainder of cycle. Consider restarting at 50mg for subsequent cycles (dose may be escalated in 50mg increments).

Thalidomide – MHRA alert: viral reactivation and pulmonary hypertension :
- Cases of viral reactivation have been reported in patients previously infected with varicella-zoster and Hepatitis B. Previously infected patients should be closely monitored for signs and symptoms or reactivation throughout treatment.
- Cases of pulmonary hypertension have been reported following thalidomide treatment. Patients should be closely monitored for signs and symptoms of cardiopulmonary disease.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Thromboembolism
Teratogenic (thalidomide)
Nephrotoxicity
Pneumonitis
Psychosis

- **Frequently occurring side effects**

Myelosuppression
Constipation, diarrhoea
Nausea and vomiting
Fatigue
Sedation
Peripheral neuropathy
Headache
Sleep disturbance,
Haemorrhagic cystitis
High blood sugars
Fluid retention

- **Other side effects**

Altered LFTs
Confusion
Depression
Alopecia

Significant drug interactions – for full details consult product literature/ reference texts

Cyclophosphamide:
Cytochrome P450 enzyme inducers (e.g. rifampicin, carbamazepine, phenytoin, St Johns Wort, corticosteroids): may increase active cyclophosphamide metabolites.
Allopurinol, Cimetidine and protease inhibitors: may increase active metabolites**.**
Aprepitant, Ciprofloxacin, Fluconazole, Itraconazole: may reduce activation of cyclophosphamide and alter the effectiveness of treatment.
Grapefruit juice: decreased or delayed activation of cyclophosphamide. Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose.

Thalidomide:
Hormonal contraceptives: may increase risk of thrombo-embolic disease – not recommended
Sedative medication: may enhance sedative effect

Additional comments

Patients should be informed not to donate blood or semen during or within 8 weeks of stopping thalidomide treatment.

References

- Summary of Product Characteristics: Cyclophosphamide (Baxter) accessed 15 June 2016 via www.medicines.org.uk
- Summary of Product Characteristics Thalidomide (Celgene) accessed 15 June 2016 via www.medicines.org.uk
- Garcaa-Sanz R, Gonzalez-Porras JR, Hernandez JM et Al. The oral combination of thalidomide, cyclophosphamide and dexamethasone is effective in relapsed/refractory multiple myeloma. Leukaemia 2004 Apr;18(4):856-863
- Kyriakou C, et al. Low-dose thalidomide in combination with oral weekly cyclophosphamide and pulsed dexamethasone is a well tolerated and effective regimen in patients with relapsed and refractory multiple myeloma. Br J Haematol. 2005 Jun;129(6):763-70

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