DT-PACE

Indication
Relapsed/refractory myeloma pre-autologous transplant
Progressive myeloma post autologous BMT

ICD-10 codes
Codes with a prefix C90

Regimen details

Day	Drug	Dose	Route
1 to 4	Dexamethasone	40mg OM	PO
1-28 (continuously)	Thalidomide	50 -400mg ON*	PO
1 to 4	Cisplatin	10mg/m^2/day (total 40mg/m^2)	Continuous IV infusion
1 to 4	Etoposide	40mg/m^2/day (total 160mg/m^2)	Continuous IV infusion
1 to 4	Cyclophosphamide	400mg/m^2/day (total 1600mg/m^2)	IV
1 to 4	Doxorubicin	10mg/m^2/day (total 40mg/m^2)	Continuous IV infusion

* thalidomide should be initiated at a dose of 50mg ON and may be increased as tolerated.

Cycle frequency
28 days

Number of cycles
Up to a maximum of 3-6 cycles

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

Thalidomide is available as 50mg capsules. The capsules should be swallowed whole in the evening.

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). If a woman thinks she may be pregnant she must stop taking thalidomide immediately.

Administration is subject to local variation.
Cyclophosphamide may be given as an IV bolus or continuous IV infusion on days 1-4.

Cisplatin, etoposide and doxorubicin are administered by continuous IV infusion over days 1-4.

Hydration is required to run concurrently. Minimum 1000mL sodium chloride 0.9% with 20mmol potassium chloride and 2g magnesium sulphate over 24 hours for on days 1-4.

Pre-medication
None required

Emetogenicity

This regimen has high emetic potential

Additional supportive medication

Allopurinol 300mg OD during cycle 1 (100mg if creatinine clearance <20ml/min)
Antiviral and PCP prophylaxis as per local policy
Antibiotic prophylaxis as per local neutropenic sepsis guidelines
PPI or H_2-antagonist as per local policy
Mouthwashes if required
GCSF SC OD from day 5 until neutrophils >1.0 x 10^9/L on 2 consecutive days.
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

Cisplatin is an exfoliant (Group 4)
Etoposide is an inflammatant (Group 2)
Cyclophosphamide is neutral (Group 1)
Doxorubicin is a vesicant (Group 5)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	7 days
U+Es (including creatinine)	7 days
LFTs	7 days
Glucose	7 days
Pregnancy test (if child bearing potential)	3 days
HIV, hepatitis B and C status	7 days
ECG	7 days
Echocardiogram	7 days

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	72 hours
U+Es (including creatinine)	72 hours
LFTs	72 hours
Glucose	72 hours
Serum paraprotein and light chains	For assessment of response prior to each cycle
Pregnancy test (if child bearing potential)	3 days

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	≥100 x 10^9/L*
CrCl	> 60mL/min
AST/ALT	< 1.5 x ULN
Bilirubin	< 1.5 x ULN

*May go ahead if cytopenias likely due to marrow involvement (consultant decision)

Dose modifications

- **Haematological toxicity**

If neutrophils < 1.0 x 10^9/L and/or platelets <100 x 10^9/L delay subsequent cycle until resolved.

- **Renal impairment**

CrCl (mL/min)	**Cisplatin dose**	**Etoposide dose**
≥60	100%	100%
50-59	75%	100%
40-49	50%	75%
16-39	Contraindicated	75%
≤15	Contraindicated	50%

* if CrCl > 20mL/min consider carboplatin – discuss with consultant.

Consider reducing cyclophosphamide dose to 75% if CrCl 10-20mL/min or 50% if CrCl < 50mL/min.

- **Hepatic impairment**

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Etoposide dose**
<1.5	and	< 1.5	100%
1.5-3.0	or	1.5-3.0	50%
>3.0	or	> 3.0	25% or omit (consultant decision)

Bilirubin (x ULN)		**AST/ALT** (x ULN)		**Alkaline phosphatase** (xULN)	**Doxorubicin dose**	**Cyclophosphamide dose**
< 1.5	and	≤ 1.5	and	≤ 2.5	100%	100%
1.5 - 3	or	1.5-3.5	or	2.5-5	50%	100%
3 - 5	or	> 3.5	and	5-10	25%	Discuss with consultant
> 5			or	> 10	Omit	Not recommended (discuss with consultant)

- **Other toxicities**

For any grade ≥ 3 non-haematological toxicity, withhold the next cycle until resolved to grade ≤ 2 and then consider restarting at 50-75% doses.

Doxorubicin

If LV ejection fraction <40% consider omitting doxorubicin (consultant decision).

Thalidomide

Toxicity	**Definition**	**Dose adjustment**
Peripheral neuropathy	Grade 3-4	Stop thalidomide (usually permanently). If symptoms resolve consider starting at 50mg for subsequent cycles (dose may be escalated in 50mg increments)
	Grade 1-2	Reduce thalidomide dose by 50% and consider discontinuing.
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
Cardiac failure
Peripheral neuropathy
Thromboembolism
Psychosis
Teratogenicity

- **Frequently occurring side effects**

Myelosuppression
Peripheral neuropathy
Lethargy, sedation
Rash
Fatigue
Tremor
Mucositis
Nausea, vomiting
Constipation, diarrhoea
InsomniaHigh blood sugars
Fluid retention
Dyspepsia

- **Other side effects**

Hypophosphataemia
Hypocalcaemia

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

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Cyclophosphamide:
Amiodarone: increased risk of pulmonary fibrosis – avoid if possible
Clozapine: increased risk of agranulocytosis – avoid concomitant use
Digoxin tablets: reduced absorption – give as liquid form
Indapamide: prolonged leucopenia is possible - avoid
Itraconazole: may increase adverse effects of cyclophosphamide
Phenytoin: reduced absorption - may need to increase dose of phenytoin
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.

Cisplatin:
Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity when given within 2 weeks of cisplatin.
Diuretics: increased risk of nephrotoxicity and ototoxicity
Nephrotoxic drugs: increased nephrotoxicity ; not recommended
Ototoxic drugs: increased risk of ototoxicity
Phenytoin: cisplatin reduces absorption and efficacy of phenytoin, monitor levels and adjust dose as necessary.
Anti-gout agents: cisplatin may increase plasma concentration of uric acid therefore dose adjustments may be required to control hyperuricaemia and gout.
Lithium: cisplatin may affect lithium plasma levels – monitor.

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

Additional comments

Stem cells have been successfully collected after DT-PACE cycle 1 or 2. Early referral for harvest is recommended.

Women of child bearing potential and males must use contraception as outlined by a MHRA approved Risk Management Program.

Doxorubicin has a life time maximum cumulative dose of 450mg/m^2

References

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