VDT-PACE

Indication
Relapsed/refractory myeloma

Primary plasma cell leukaemia – induction therapy

Note: funding for bortezomib must be agreed prior to commencing treatment.

ICD-10 codes
Codes with a prefix C90

Regimen details

Day	Drug	Dose	Route
1 to 4	Dexamethasone	40mg OM	PO
1, 4, 8, and 11	Bortezomib	1.0mg/m^2	SC
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.

At least 72 hours must elapse between doses of bortezomib

Cycle frequency
28 days

Number of cycles
Up to a maximum of 2-4 cycles

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

Bortezomib is administered by SC injection. At least 72 hours must elapse between doses of bortezomib.

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 once a month during treatment continuing 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 low molecular weight heparin (LMWH) or direct oral anticoagulant (DOAC) (as applicable within NICE guidance).

Extravasation
Cisplatin is an exfoliant (Group 4)
Etoposide is an inflammatant (Group 2)
Cyclophosphamide and bortezomib are 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
Blood pressure (lying and standing)	On day 1
ECG	7 days
Echocardiogram	7 days

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

Investigations – pre subsequent cycles

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

Serum electrophoresis (or alternative biological measure of response if M protein not measurable)
Clinical assessment for neuropathy

* Additional FBC monitoring is required as below:
For patients with platelet count at cycle pre-assessment > $70x10^9$/L the risk of severe thrombocytopenia is low. Check FBC before each dose but administer the drug without waiting for the result. If the platelets are subsequently found to be low, then consider a repeat FBC 48 hours later and the need for platelet transfusion.
In patients with platelet count < $70x10^9$/L at cycle pre-assessment, the drug should be withheld until the FBC is known and the dose omitted if the platelets are < 25 $x10^9$/L. Unless the thrombocytopenia is due to marrow infiltration by myeloma; consider proceeding with treatment with platelet transfusion support.

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	< 2 x ULN
Bilirubin	< 1.5 x ULN

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

Dose modifications

Doses of bortezomib are modified according to the following table:

Full dose	1.0mg/m^2
First dose reduction	0.7mg/m^2
Second dose reduction	0.5 mg/m^2

On days 4, 8 and 11 if neutrophils ≤ 0.75 x 10^9/L **or** platelets ≤ 30 x 10^9/L withhold bortezomib. If several doses within a cycle are withheld, consider dose reduction of bortezomib for subsequent cycles.

See above for FBC monitoring requirements.

- **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.

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

Bortezomib:
If CrCl < 20mL/min use with caution

- **Hepatic impairment**

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Doxorubicin dose**	**Cyclophosphamide dose**	**Etoposide dose**
< 1.5	and	≤ 1.5	100%	100%	100%
1.5 - 3	or	1.5- 3	50%	100%	50%
3 - 5	or	> 3.0	25%	Discuss with consultant	25% or omit
> 5			Omit	Not recommended (discuss with consultant)	Omit

Bortezomib:
If bilirubin > 1.5 x ULN consider starting dose of 0.7mg/m^2 for cycle 1. For subsequent cycles increase dose to 1mg/m^2 or reduce dose to 0.5mg/m^2 according to tolerability.

- **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.

Bortezomib:

Toxicity	**Definition**	**Bortezomib dose**
Neuropathy	Grade 1 with no pain	100%
	Grade 1 with pain or grade 2 but not interfering with daily living	0.7mg/m^2
	Grade 2 with pain or grade 3	Withhold until symptoms resolved Restart at dose of 0.5mg/m^2
	Grade 4	Discontinue

Any other ≥ grade 3 non-haematological toxicity: withhold bortezomib until ≤ grade 1. Recommence with 1 level dose reduction.

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

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
Cardiac failure
Peripheral neuropathy
Thromboembolism
Orthostatic hypotension
Psychosis
Teratogenicity

- **Frequently occurring side effects**

Myelosuppression
Peripheral neuropathy
Lethargy, sedation
Rash
Fatigue
Tremor
Mucositis
Nausea, vomiting
Constipation, diarrhoea
Insomnia
High blood sugars
Fluid retention
Dyspepsia
Blepharitis
Autonomic neuropathy

- **Other side effects**

Hypophosphataemia
Hypocalcaemia
Dizziness

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.

Bortezomib:
Antihypertensives: Risk of additive hypotensive effect. Close monitoring of BP is required.
Oral anti diabetic agents: Hyper and hypo glycaemia has been reported. Close monitoring of blood glucose is required.
Ciclosporin: increased risk of severe neuropathy: avoid concomitant use.
High dose vitamin C: reduced efficacy of bortezomib: avoid concomitant use.
Cytochrome P34A inhibitors (ketoconazole and other azole antifungals, clarithromycin, erythromycin) may increase bortezomib levels: avoid concomitant use.

Cytochrome P34A inducers (rifampicin, carbamazepine, phenytoin, St Johns Wort) may reduce bortezomib levels: avoid concomitant use.

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

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

Women of child bearing potential and males must use contraception as outlined by a MHRA approved Risk Management Program.
Patients should be informed not to donate blood or semen during or within 8 weeks of stopping thalidomide treatment.

References

- Lee C-K et al. DT-PACE: An effective, novel combination chemotherapy with thalidomide for previously treated patients with myeloma. J Clin Oncol. 2003;21;2732-2739
- Srikanth M. et al Survival and outcome of blastoid variant myeloma following treatment with the novel thalidomide containing regime DT-PACE. E J Haem 2008;81;432-436
- Summary of Product Characteristics Cyclophosphamide accessed 21 Jan 2015 via http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs
- Summary of Product Characteristics: Bortezomib (Janssen) accessed 7 Dec 16 via www.medicines.org.uk
- Summary of Product Characteristics Etoposide (Medac) accessed 21 Jan 2015 via www.medicines.org.uk
- Summary of Product Characteristics Thalidomide (Celgene) accessed 21 Jan 2015 via www.medicines.org.uk
- Summary of Product Characteristics Doxorubicin (Hospira) accessed 21 Jan 2015 via www.medicines.org.uk
- Summary of Product Characteristics Cisplatin (Hospira) accessed 21 Jan 2015 via www.medicines.org.uk
- MHRA alert accessed 27 July 2016 via https://www.gov.uk/drug-safety-update/letters-sent-to-healthcare-professionals-in-june-2016

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