VDTPACE/ DTPACE

INDICATIONS

Failure to achieve response or disease progression with induction therapy

Relapsed or refractory myeloma patients suitable for intensive salvage chemotherapy.

Primary plasma cell leukaemia or initial presentation with extra-medullary disease.

This protocol covers VDTPACE/DTPACE and when carboplatin is used instead of cisplatin (i.e. in case of renal impairment). Ensure the correct protocol is selected on the electronic prescribing system when prescribing.

TREATMENT INETENT

Disease modification

GENERAL PRE-ASSESSMENT

1. Ensure all the following staging investigations are done:
   - FBC & film
   - Clotting screen
   - U&Es
   - LFTs
   - Calcium
   - Albumin
   - Uric acid
   - CRP
   - Baseline random blood glucose level
   - ECG & Transthoracic echocardiogram to assess LV function if clinically indicated
   - Virology : HIV, Hepatitis B (including core antibody), and Hepatitis C
   - Calculated creatinine clearance (CrCl), urine protein/ creatinine ratio
   - Electrophoresis and immunofixation for quantitation of serum paraprotein and immunoglobulins
   - Serum free light chain assay (Freelite)
   - β_2 microglobulin
   - LDH
   - Myeloma FISH should be performed in all patients at diagnosis, and in selected patients at relapse/progression to help guide treatment decisions Samples should be sent to Wessex Regional Genetics Laboratory (address below)
   - Irradiated blood products should be used from the start of the mobilization cycle
   - Group and Save
   - Serum free light chain assay
   - Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle
   - Imaging as per NICE/network guidance and clinical presentation
   - Bone marrow aspirate and trephine (with immunophenotyping for kappa/lambda if appropriate)

Wessex Regional Genetic Laboratory
Salisbury NHS Foundation Trust
Salisbury Disctrict Hospital
Salisbury
Wiltshire
SP2 8BJ

2. If allogeneic transplant an option: Tissue typing of patient and siblings and CMV serology
3. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent for the treatment.
4. Fertility - all patients should be offered fertility advice, as appropriate.
5. Hydration - fluid intake of at least 3 litres /day should be attempted.
6. Document patient's height and weight It is reasonable to consider capping at BSA of 2 m^2 in selected patients
7. Document patient's performance status.
8. Treatment must be agreed at the relevant MDT.

REGIMEN SPECIFIC PRE ASSESSMENT

IMPORTANT: EXTRAVASATION RISK
THIS REGIMEN CONTAINS VESICANTS. WHICH MUST ONLY BE ADMINISTERED VIA CENTRAL VENOUS CATHETER.

- . At least a double lumen central venous access and a double lumen midline.
- The conditions of the Thalidomide Pregnancy Prevention Programme must be fulfilled for all male and female patient
- Clinical assessment of thrombo-embolic risk.
- Evaluate for presence of neuropathy.

DRUG REGIMEN

Depending on stability data used by the different hospitals, the protocol lists 2 options: the first is combining daily cisplatin/etoposide/cyclophosphamide into the same 24-hour infusion bag. The second option is: combining daily cisplatin/etoposide in the same 24-hour infusion bag, but cyclophosphamide is given separately as a bolus

Days	Drug	Dose	Route	Comments
1 to 4	**Dexamethasone**	40 mg daily	Oral	
Continuous daily/ If PBSC harvest planned only for days 1 to 4	**Thalidomide (See note below)**	Start 50 mg and increase up to 100 mg as tolerated	Oral	ONCE daily at NIGHT
1 to 4	**Cisplatin ***	10 mg/m^2/day [total dose per cycle 40 mg/m^2]	Continuous intravenous infusion through central line	Daily dose of Cisplatin and Etoposide combined in a 1 litre 0.9% sodium chloride bag and infused over 24 hours (if cyclophosphamide is given separately as a bolus) OR Daily dose of Cisplatin, Etoposide in addition to cyclophosphamide, combined in a 1 litre 0.9% sodium chloride bag and infused over 24 hours (if cyclophosphamide is given as a continuous infusion)
1 to 4	**Hydration**	1L 0.9% sodium chloride with 20 mmol KCl (potassium chloride) and 8 mmol magnesium sulphate 12 hourly	Continuous intravenous infusion through midline	Continuous intravenous infusion
1 to 4	**Etoposide ***	40 mg/m^2/day [total dose per cycle 160 mg/m^2]	Continuous intravenous infusion through central line	Daily dose of Cisplatin and Etoposide combined in a 1 litre 0.9% sodium chloride bag and infused over 24 hours (if cyclophosphamide is given separately as a bolus) OR Daily dose of Cisplatin, Etoposide in addition to cyclophosphamide, combined in a 1 litre 0.9% sodium chloride bag and infused over 24 hours (if cyclophosphamide is given as a continuous infusion)

1 to 4	**Cyclophosphamide***	400 mg/m^2/day [total dose per cycle 1600 mg/m^2]	Intravenous Bolus injection OR Continuous intravenous infusion through central line	Daily dose of cyclophosphamide administered as a bolus injection OR Daily dose of Cisplatin, Etoposide in addition to cyclophosphamide, combined in a 1 litre 0.9% sodium chloride bag and infused over 24 hours (if cyclophosphamide is given as a continuous infusion)
1 to 4	**Doxorubicin ***	10 mg/m^2/day [total dose per cycle 40 mg/m^2]	Continuous intravenous infusion **must be through a central line**	Daily dose of doxorubicin In 100 ml of sodium chloride 0.9% and infused over 24 hours
Day 6	**GCSF**	Filgrastim 0.5 miu/kg daily from day 6 until neutrophils > 1.0 x 10^9/L. Filgrastim 1 miu/kg from days 6 onwards if harvesting PBSCs, with aim to collect on days 15 – 16. Filgrastim to start 24 hours after the completion of chemotherapy (The D4 24 hour chemotherapy infusion is completed on D5, hence start of filgrastim is 24 hours after that i.e. D6)		
1, 4, 8 and 11	**Bortezomib**	1.0 mg/m^2	S/C bolus	**“”Only where Bortezomib is indicated””**
* It is reasonable to consider capping at BSA of 2 m^2 in selected patients				

If carboplatin is indicated instead of Cisplatin (i.e. in view of renal impairment), regimen is as follows;

Days	Drug	Dose	Route	Comments
1 to 4	**Dexamethasone**	40 mg daily	Oral	
Continuous daily/ If PBSC harvest planned only for days 1 to 4	**Thalidomide (See note below)**	Start 50 mg and increase up to 100 mg as tolerated	Oral	ONCE daily at NIGHT
1 to 4	**Carboplatin***	50 mg/m^2/ day	Continuous intravenous infusion central line	Daily dose of carboplatin in 500ml glucose 5% bag and infused over 24 hours
1 to 4	**Etoposide ***	40 mg/m^2/day [total dose per cycle 160 mg/m^2]	Continuous intravenous infusion through central line	Daily dose of etoposide in a 250ml sodium chloride 0.9% bag and infused over 24 hours
1 to 4	**Cyclophosphamide***	400 mg/m^2/day [total dose per cycle 1600 mg/m^2]	Continuous intravenous infusion through central line OR Intravenous Bolus injection	Continuous IV infusion over 24 hours (preferable option) OR Daily dose of cyclophosphamide administered as a bolus injection
1 to 4	**Doxorubicin ***	10 mg/m^2/day [total dose per cycle 40 mg/m^2]	Continuous intravenous infusion **Must be through a central line**	Daily dose of doxorubicin In 100 ml of sodium chloride 0.9% and infused over 24 hours
Day 6	**GCSF**	Filgrastim 0.5 miu/kg daily from day 6 until neutrophils > 1.0 x 10^9/L. Filgrastim 1 miu/kg from days 6 onwards if harvesting PBSCs, with aim to collect on days 15 – 16.		

		Filgrastim to start 24 hours after the completion of chemotherapy (The D4 24 hour chemotherapy infusion is completed on D5, hence start of filgrastim is 24 hours after that i.e. D6)		
1, 4, 8 and 11	**Bortezomib (If Indicated)**	1.0 mg/m^2	S/C bolus	**“”Only where bortezomib is indicated””**
* It is reasonable to consider capping at BSA of 2 m^2 in selected patients				

CYCLE FREQUENCY

Cycle frequency: every 4-6 weeks. Total number of cycles 2-4.
Thalidomide can be omitted on clinician’s discretion if disease is assessed to be Thalidomide resistant.

DOSE MODIFICATIONS

Haematological:

- Where cytopenias are considered to be chemotherapy induced delay subsequent cycles until neutrophils > 1 x 10^9/L and platelets > 70 x 10^9/L .
- Where cytopenias are secondary to bone marrow infiltration dose modification may not be indicated- clinical decision.
- Discuss with consultant management of grade 3 and 4 haematological toxicities.

Renal/hepatic impairment

Thalidomide:

Renal	Hepatic
No dose reduction necessary	No dose reduction necessary

Cisplatin:

Renal	Hepatic
GFR > 60 ml/min 100% dose GFR 45 – 59 ml/min 75% dose GFR < 45 ml/min: Consider carboplatin at 50 mg/m^2/ day Days 1-4.	No dose reduction necessary

Doxorubicin:

Renal	Hepatic	
GFR>10mL/min: no dose adjustment is needed GFR<10mL/min: no need for dose adjustment is expected Hemodialysis: 75% of the original dose may be considered	Bili 20 – 50 Bili 51 – 86 Bili > 86 or Child-Pugh C	50% dose 25% dose Omit
Cumulative max dose of Doxorubicin: 450-550 mg/m². Prior radiotherapy to the mediastinal / pericardial area 400 mg/m².		

Cyclophosphamide:

Renal	Hepatic
According to GFR (mL/min): ≥30: 100% dose 10-29: 75% dose <10: Not recommended, if unavoidable consider 50% dose Hemodialysis: Not recommended, if unavoidable consider 50% dose	Mild and moderate: no need for dose adjustment is expected. Severe: not recommended, due to risk of reduced efficacy. Discuss with Consultant

Etoposide:

Renal	Hepatic
GFR > 50 ml/min 100% dose GFR 15 – 50 ml/min 75% dose GFR < 15 ml/min 50% dose Subsequent doses should be based on clinical response	Bili 26-51 or AST 60-180 50% dose Bili > 51 or AST > 180 – clinical decision

Bortezomib

Renal	Hepatic
No dose reduction necessary For dialysis patients Bortezomib should be given after dialysis.	Bili >1.5x ULN reduce bortezomib to 0.7mg/m^2 in first cycle. Consider dose escalation to 1.0mg/m2 or further dose reduction to 0.5mg/m2 in subsequent cycles depending on patient tolerability.

Carboplatin

Renal	Hepatic
Dose using Calvert equation: Dose = AUC (25 + GFR) Contraindicated if CrCl <20 mL/min. Discuss with consultant	No need for dose adjustment is expected in hepatic impairment

Peripheral Neuropathy:
Bortezomib: If there are symptoms of peripheral neuropathy, the dose reduction schedule must be invoked (see below).The drug should be stopped if symptoms or signs progress despite this.

Severity of neuropathy	Posology modification
G1 with no pain or loss of function	None
G1 with pain or G2	Reduce to 0.7 mg/m^2 or Change treatment schedule to 1.0 mg/m^2 once per week

G2 with pain or G3	Withhold treatment until symptoms of toxicity have resolved. When toxicity resolves re-initiate treatment at 0.7 mg/m^2 once per week.
G4 and/or severe autonomic neuropathy	Discontinue

Thalidomide:
Thalidomide should be stopped if there are symptoms of peripheral neuropathy causing pain or functional disability (grade 2 or above). If symptoms resolve to grade 1 or better (or back to normal baseline) cautious reintroduction at a dose of 50mg should be considered, escalating in 50mg increments as symptoms permit

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INVESTIGATIONS

- Urine pregnancy testing for pre-menopausal women younger than 55 before each cycle.
- FBC & U&E's, Ca^{++}, LFTs
- Ig's, paraprotein, urinary BJP and serum free light chain levels in patients with light chain disease - monthly.
- Clinical assessment of neuropathy

CONCURRENT MEDICATIONS

- Allopurinol 300 mg daily for 7 days for cycle 1 only.
- Prophylactic aciclovir 200 mg TDS (consider reducing to 200mg BD if CrCl<10ml/min) for the duration of treatment and 3 months post therapy
- Prophylactic fluconazole 50mg OD
- Consider prophylactic co-trimoxazole 960mg OD on M/W/F if heavily pre-treated or previous autograft.
- Proton pump inhibitor or H_2 anagonist at clinician's discretion.
- Thromboprophylaxis/anticoagulation- see VTE section below
- Filgrastim 0.5 miu/kg from day 6 until neutrophils > 1.0 on two consecutive days. Filgrastim 1 miu/kg from days 6 onwards if harvesting PBSCs, with aim to collect on days 15 – 16.
- Bone protection as per NSSG Bone Protection protocol MM.3

Patients on bortezomib should be closely monitored if on CYP3A4-inhibitors (e.g. ketoconazole, ritonavir). The concomitant use of bortezomib with strong CYP3A4-inducers (rifampicin, carabamazepine, phenytoin, phenobarbital, and St John's wort) is not recommended as efficacy may be reduced.

EMETIC RISK

High emetic risk on days 1-4, otherwise minimal or low.

EXTRAVASATION RISK

Doxorubicin- **Vesicant**
Cisplatin- Exfoliant
Etoposide- Inflammatory
Cyclophosphamide- Neutral
Carboplatin- Irritant

ADVERSE EFFECTS/REGIEMN SPECIFIC COMPLICATIONS

- **Myelosuppression:** including neutropenia and thrombocytopenia. Follow dose modifications for haematological toxicity as per section above.
- **Teratogenic**: The relevant Pregnancy Prevention Programme must be observed for all male and female patients. Prescribing and dispensing of thalidomide must be in line with the pregnancy prevention programme.
- **Peripheral neuropathy:** Patients should be advised to report pain hypersensitivity prickling, numbness and paraesthesia. If these occur see above dose reductions and consider use of Amitriptyline, Gabapentin and Pain Team referral. Neuropathy assessment tools are available in DTU. Caution in patients with existing peripheral neuropathy
- **Venous thromboembolism (VTE):** There is an increased risk of thrombosis with thalidomide. Unless the patient is thought to be at particularly low-risk of thrombosis or high-risk of bleeding, some form of VTE prophylaxis is recommended as follows:

  1. Prophylactic low-molecular weight heparin OR
  2. Prophylactic NOAC e.g. apixaban 2.5mg bd (check product specific information)

  Aspirin can be appropriate for patients with no additional risk factors for thrombosis. It is generally not preferred for higher-risk patients with additional risk factors

  If VTE occurs, thalidomide can be continued and the patient should be fully anticoagulated according to standard guidelines.

- **Cyclophosphamide may irritate the bladder mucosa**. Patients should be encouraged to drink a minimum of three litres of fluid per 24 hours. Monitor for signs of bladder irritation and ensure adequate hydration with mesna rescue in case of symptoms.
- **Cardiotoxicity** - monitor cardiac function. Doxorubicin may be stopped in future cycles if signs of cardiotoxicity, e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue.
- **Cisplatin** – Nephrotoxicity and ototoxicity
- **Steroids** – Monitor BMs

TREATMENT RELATED MORTALITY

5-10 %

REFERENCES

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6. North West London Cancer Network. DTPACE v 1 3 Jul09 (2) protocol. Available online on: http://www.londoncanceralliance.nhs.uk/media/42754/3%2013%20DTPACE%20v%201%203%20Jul09%20(2).pdf
7. Bortezomib (Velcade®) eMC UK Summary of Product Characteristics, Janssen, March 2017

Name	Revision	Date	Version	Review date
Nadjoua Maouche (haematology pharmacist) Dr Karthik Ramasamy (Consultant Haematologist) Rachel Miller (Deputy Matron)	Amalgamation of previous version of VDTPACE and DTPACE. Added Extravasation information, added carboplatin regime. Updated line access. Separated chemotherapy administration due to stability.	March 2019	1.0	June 2020
Faouzi Djebbari (Haematology Pharmacist) Dr Karthik Ramasamy (Consultant Haematologist)	Revised chemotherapy administration due to stability	July 2019	1.1	June 2020
NSSG Myeloma Group	Filgrastim clarification (to start D6)	Nov 2020	1.2	June 2021
NSSG Myeloma Group	Updated protocol with clarification on possible combinations of chemotherapy infusion bags depending on stability	Dec 2021	2.0	June 2022
NSSG Myeloma Group	Annual protocol review, updated sections for renal and hepatic impairmen	June 2022	2.1	June 2023

REVIEW