DT - PACE

Refractory and/or relapsed myeloma in a patient suitable for intensive chemotherapy

Drugs/Dosage/
Administration: Intravenous drugs to be given via a central line with a triple lumen

Day	Drug	Dose	Administration
Days 1, 2, 3 & 4 (Line 1)	Cyclophosphamide	400mg/m^2/24hr	all combined in 1000ml 0.9% sodium chloride and administered by continuous IV infusion over 24 hours
	Etoposide	40mg/m^2/24hr	
	Cisplatin	10mg/m^2/24hr	
Days 1, 2, 3 & 4 (Line 2)	Doxorubicin	10mg/m^2/24hr	in 100ml 0.9% sodium chloride and administered by continuous IV infusion over 24 hours
Days 1, 2, 3 & 4 (Line 3)	0.9% sodium chloride 1000ml + 20mmol KCl + 10mmol $MgS0_4$		IV infusion over 24 hours (hydration for cisplatin)
Days 1, 2, 3 & 4	Dexamethasone	40mg once daily, in the morning, with food	oral
Continuous once daily	Thalidomide	Start at 50mg and increase up to 100mg as tolerated; once daily at bedtime	oral
Start on Day 6	G-CSF	once daily, as Alliance G-CSF guidelines, until neutrophil recovery	s/c bolus

Other drugs: Allopurinol (dose according to renal function) – review after 4 weeks
PCP prophylaxis – prescribe according to unit practice/protocol
Use of PPI or ranitidine is recommended whilst treating with steroids
Thromboprophylaxis for patients on thalidomide, according to unit practice, is recommended in the absence of specific contraindication.
Fluconazole 100mg od for antifungal prophylaxis
Aciclovir prophylaxis (400mg bd) if previous history of herpes simplex infection
Norethisterone 5mg tds - pre-menopausal women only
Laxative as required for thalidomide-induced constipation

Frequency: usually 2 cycles
4 – 6 week cycle, according to blood recovery

Main Toxicities: teratogenicity (see Comments); sedation (take thalidomide at bedtime); dizziness; constipation (often requiring laxatives); dry skin or rash; peripheral neuropathy (see Comments); increased risk of thromboembolic events; steroid side effects

Anti- emetics:	highly emetogenic (but anti-emetic doses of dexamethasone not required while on high dose dexamethasone)	
Extravasation:	doxorubicin is a vesicant	
Regular Investigations:	FBC	Day 1, then three times weekly
	U&Es	Day 1, then three times weekly
	LFTs	Day 1, then once weekly
	Serum sample for protein electrophoresis, paraprotein and serum free light chains	Day 1
	Pregnancy test	every 4 weeks for women of child bearing potential
	Blood glucose monitoring	see Comments
	Blood pressure monitoring	see Comments
	MUGA/echo	see Comments
	Cr^{51}-EDTA or 24hr urine collection	baseline (see Comments)

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

Maximum cumulative dose of doxorubicin = 450 - 550mg/m^2. Consider previous anthracycline exposure.
A baseline MUGA / echo should be performed where the patient is considered at risk of having impaired cardiac function e.g. significant cardiac history, hypertension, obese, smoker, ≥ 70 years old, previous exposure to anthracyclines, previous thoracic radiotherapy. MUGA /echo should be repeated if there is suspicion of cardiac toxicity at any point during treatment.

For patients on Cycle 1 whose Cr^{51}-EDTA / 24 hour urine result is not yet available, Cockcroft & Gault may be used to predict GFR. Cisplatin dose should be adjusted if necessary once results available. Repeat Cr^{51}-EDTA / 24 hour urine only if the result is borderline at the start of treatment or if there is a 30% change in serum creatinine.

Check electrolytes – additional supplements of magnesium, potassium or calcium may be required.

Weight should be recorded daily during cisplatin treatment, and a strict fluid balance chart should be maintained. An average urine output of at least 100ml/hr must be maintained throughout treatment. If the urine output is inadequate, the patient should be assessed and urine output increased by administering 500ml sodium chloride 0.9% IV +/- furosemide 40mg. Furosemide 20 – 40mg po may also be given if there is a positive fluid balance of 1.5 litres, a weight gain of 1.5kg or symptoms of fluid overload.

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:

Proceed once neutrophils > 1.0 x 10^9/L and platelets > 100 x 10^9/L.
Delay in count recovery after treatment should be managed according to local protocols / practice.
Interrupt thalidomide if platelets < 30 x 10^9/L

Renal Impairment:

CrCl (ml/min)	Cisplatin Dose
> 50	Give 10mg/m^2/24hr
30 – 50	Give 5mg/m^2/24hr
< 30	Contra-indicated

Refer to the tables for cyclophosphamide and etoposide below, but discuss with Consultant before any dose reductions are made:

CrCl (ml/min)	Cyclophosphamide Dose
> 20	Give 100% dose
10 – 20	Give 75% dose
< 10	Give 50% dose

CrCl (ml/min)	Etoposide Dose
> 50	Give 100%
15 – 50	Give 75%
< 15	Give 50%

Hepatic Impairment:

Refer to the table below for doxorubicin, but discuss with Consultant before any dose reductions are made.

ALT / AST	Bilirubin (µmol/l)	Doxorubicin Dose
2 – 3 x ULN	-	Give 75%
> 3 x ULN **or**	20 – 51	Give 50%
	51 – 85	Give 25%
	> 85	Omit

Creatinine clearance is the strongest predictor of etoposide clearance. There is conflicting information about dose reduction with hepatic impairment. Use the table below, but again discuss with Consultant before any dose reductions are made.

Bilirubin (μmol/l)		AST (units/l)	Etoposide Dose
26 – 51	**or**	60 – 180	Give 50% dose
> 51	**or**	> 180	Clinical decision

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.

Patient Information:

Macmillan leaflets for Cisplatin, Etoposide, Cyclophosphamide, Doxorubicin and Thalidomide
Pharmion Pregnancy Prevention Programme Booklet

References:

Lee, C et al; JCO 2003; 21 (14): 2732 – 2739
Srikanth, M et al; Eur J Haematol 2008; 81: 432 – 436