Bendamustine, Thalidomide and Dexamethasone (BTD)

For relapsed multiple myeloma

Blueteq registration is required before treatment may start

Patients should be monitored throughout treatment for opportunistic infections, in line with MHRA alert July 2017
(https://www.gov.uk/drug-safety-update/bendamustine-levact-increased-mortality-observed-in-recent-clinical-studies-in-off-label-use-monitor-for-opportunistic-infections-hepatitis-b-reactivation)

Drugs/Dosage:	**Bendamustine**	60mg/m^2	IV	Day 1 and Day 8
	Thalidomide	initial dose 50mg po daily, titrating upwards every 2 weeks to a maximum of 200mg daily, depending on tolerability		
	Dexamethasone	40mg po once daily in the morning on Days 1, 8, 15 and 22 (Dexamethasone 40mg po om on Days 1 – 4 and Days 15 - 18 if require rapid cytoreduction in Cycle 1)		

Administration: Bendamustine in 500ml sodium chloride 0.9% and infused over 30 minutes.
IV antihistamine and steroid cover should be considered with subsequent bendamustine doses for patients who experience even a mild hypersensitivity reaction on Cycle 1. It is suggested that reactions ≥ Grade 3 should not be rechallenged.

Thalidomide is available as 50mg capsules. The daily dose should be taken at bedtime to avoid problems with day-time sedation. Patients should be advised not to drive or operate machinery for 8 hours after each dose.

Dexamethasone to be taken in the morning with or after food

Other drugs: Allopurinol (dose according to renal function) – review after 4 weeks
Omeprazole 20mg od (or ranitidine) is recommended whilst treating with steroids
Laxative as required for thalidomide-induced constipation
Thromboprophylaxis, according to unit practice, is recommended in the absence of specific contraindication
Aciclovir 400mg bd
Co-trimoxazole 480mg od throughout treatment and until lymphocyte count > 1 x 10^9/l
Fluconazole 100mg po od as antifungal prophylaxis

Frequency: 4 weekly cycle, for a minimum of 6 cycles or until best response plus 2 cycles, up to a maximum of 9 cycles.

Main Toxicities: myelosuppression; bendamustine hypersensitivity reactions eg. rash, urticaria (see Comments); sedation (take thalidomide at bedtime); dry skin or rash; teratogenicity (see Comments); peripheral neuropathy; dizziness; bradycardia and syncope; alopecia; constipation (often requiring laxatives); increased risk of thromboembolic events; steroid side effects

Anti- emetics: Days 1 and 8 - highly emetogenic
(N.B. due to high dose dexamethasone, anti-emetic doses of dexamethasone are not required)

Reason for Update: supportive meds reviewed / MHRA alert added	Approved by Chair of Alliance TSSG: Dr A Laurie
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Supersedes: Version 1	Review Date: Sept 2019
Prepared by: S Taylor	Checked by: C Tucker

Regular Investigations:	FBC	at least every 4 weeks, more frequently if indicated
	U&Es & LFTs	every 4 weeks
	Paraprotein and/or serum free light chains	every 4 weeks
	Pregnancy test	every 4 weeks for women of child bearing potential
	Blood glucose monitoring	see Comments
	Blood pressure monitoring	see Comments

Comments: All patients must receive irradiated blood products for all future transfusions - inform patient and blood bank.

While on dexamethasone, blood glucose and blood pressure monitoring to be tailored according to individual patient needs.

Due to previous reports of cardiac side-effects with bendamustine (e.g. heart failure, arrhythmias, hypotension), use with caution if patient has pre-existing heart disease (e.g. myocardial infarction, severe cardiac arrhythmias). In such cases the heart disease should be monitored more closely and an ECG recorded. In addition, the fluid and electrolyte balance should be monitored, paying particular attention to potassium.

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: If neutrophil count < 1.0 x 10^9/L or platelets < 75 x 10^9/L, defer bendamustine until the counts have recovered. Continue with dexamethasone and thalidomide.

Dose reductions in bendamustine may be necessary, but there is no standard advice.

If low counts are thought to be disease-related, discuss with Consultant.

Renal Impairment: No dose adjustment for bendamustine required if CrCl > 10ml/min.

Hepatic Impairment:

Bilirubin (µmol/l)	Bendamustine dose
< 21	Give 100% dose
21 – 51	Give 70% dose
> 51	No data available

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.

Steroid Side Effects:

If severe steroid-related side effects develop, dose reduction to dexamethasone 20mg per dose may be considered, or omit one "pulse" of dexamethasone, according to individual case.

Patient Information:

Celgene Pregnancy Prevention Programme Booklet
Macmillan leaflet for Bendamustine
"Thalidomide and Myeloma" Infoguide produced by Myeloma UK is also recommended (available at www.myelomaonline.org.uk)

References:

Ramasamy, K et al; Br J Haematol 2011; 155 (5): 632 – 634
Grey-Davies, E et al; Br J Haematol 2011; 156: 552 – 554
Dosing and scheduling as UCLH practice