VEPEM-B

Indication
Hodgkin's Lymphoma in older fitter patients (> 60 years of age).

ICD-10
Codes with a prefix C 81

Regimen details

Day	Drug	Dose	Route
1	Vinblastine	6mg/m^2 (max 10mg)	IV infusion
1	Cyclophosphamide	500mg/m^2	IV
1-5	Procarbazine	100mg/m^2 OD (or in 3 divided doses)	PO
1-5	Prednisolone	30mg/m^2 OD	PO
15	Mitoxantrone	6mg/m^2	IV infusion
15	Hydrocortisone	100mg	IV bolus
15	Bleomycin	10,000 iu/m^2 (max 15,000 iu)	IV infusion
15-19	Etoposide	60mg/m^2 OD	PO

GCSF may be required as per local policy on days 6-14 and 20-27.

Cycle frequency
28 days

Number of cycles
Usually given for up to 6 cycles.

Administration
Vinblastine is administered in 50mL sodium chloride 0.9% over 10 minutes as per national guidance. Nurse to remain with patient throughout infusion.

Cyclophosphamide is administered as a slow IV bolus via a fast running drip.

Procarbazine is available as 50mg capsules. Procarbazine should be swallowed whole with water. The dose can be taken as a single dose or in three divided doses (total daily dose: 100mg/m^2). Patients must not drink alcohol while taking procarbazine (due to the risk of disulfiram type reaction).

Mitoxantrone is administered in 50mL sodium chloride 0.9% over 15 minutes.

Prior to bleomycin, hydrocortisone 100mg IV stat should be administered. Bleomycin is administered in 100mL sodium chloride 0.9% over 60 minutes.

Etoposide is available as 50mg and 100mg capsules. The dose should be rounded to nearest 50mg and swallowed whole on an empty stomach or an hour before food.

Pre-medication

Antiemetics as per local policy.
Hydrocortisone 100mg IV stat is required prior to bleomycin on day 15.

Emetogenicity

This regimen has moderate emetic potential.

Additional supportive medication

Allopurinol 300mg OD (100mg OD if CrCl < 20mL/min) for the first cycle.
Antiemetics as per local policy
Mouthwashes if required.
H_2 antagonist or proton-pump inhibitor if required (particularly during prednisolone).
Antiviral prophylaxis as per local policy.
Prophylactic antibiotics and antifungals may be required (as per local policy) during periods of neutropenia.
PCP prophylaxis during treatment and to continue until 6 months after treatment stopped.

Extravasation

Vinblastine is a vesicant
Mitoxantrone is an exfoliant
Cyclophosphamide and bleomycin are neutral

Investigations – pre first cycle

Investigation	Validity period
FBC	7 days
LDH	7 days
U+Es (including creatinine)	7 days
LFTs	7 days

Consider hepatitis B core antibody and hepatitis BsAg, hepatitis C antibody, HIV 1+2 serology.

Baseline pulmonary function tests, including transfer factor, are recommended prior to commencing bleomycin.

Consider ECG and echocardiogram if patient has significant cardiac history.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	On days 1 and 15
U+Es (including creatinine)	72 hours (prior to days 1 and 15)
LFTs	72 hours (prior to days 1 and 15)

Standard limits for administration to go ahead and dose modifications

Investigation	Limit
Neutrophils*	≥ 2.0 $x10^9$/L
Platelets*	≥ 100 $x10^9$/L
CrCl	> 50mL/min
AST/ALT	> 1.5 x ULN
Bilirubin	> ULN

* unless due to disease (splenomegaly, bone marrow infiltration)

Dose modifications

- **Haematological toxicity**

Neutrophils (x10^9/L)		**Platelets** (x10^9/L)	**Action**
> 2.0	And	> 100	100% doses
1.0-2.0	and/or	50-100	Delay 1 week until recovery then recommence with 100% doses If not recovered recommence at 50-75% dose (100% bleomycin) as long as blood counts not further reduced – consultant decision
<1.0	and/or	< 50	Discuss with consultant

- **Renal impairment**

CrCl (mL/min)	**Etoposide dose**	**Bleomycin dose**	**Cyclophosphamide dose**
> 50	100%	100%	100%
>20-50	75%	75%	
>15-20			75%
>10 - 15	50%		
<10		50%	50%

Procarbazine: if serum creatinine > 177µmol/L reduce dose to 50%.

- **Hepatic impairment**

AST/ALT (x ULN)		**Bilirubin** (x ULN)	**Vinblastine**	**Procarbazine**
< ULN	And	< 1.5	100%	100%
1-3.5	And/or	1.5-3	50%	100%
< ULN	And	3-5	50%	Consider dose reduction (consultant decision)
> 3.5	And	3-5	Omit	
> 3.5	And/or	> 5		Contraindicated

AST/ALT (x ULN)		**Bilirubin** (x ULN)	**Etoposide dose**	**Mitoxantrone dose**
< ULN	And	< ULN	100%	100%
1-3.5	And/or	1-3	50%	Consider dose reduction (consultant decision based on performance status)
>3.5	And/or	> 3	Clinical decision	

- **Other toxicities**

Toxicity	**Definition**	**Dose adjustment**
Neurological toxicity	Grade ≥ 2	Discontinue vinblastine
Cardiac toxicity	Signs or symptoms of cardiac disease LVEF < 50%	Discuss with consultant Consider dose reduction or discontinuation of treatment
Pulmonary toxicity	Signs and symptoms of pulmonary toxicity Diffusing capacity < 50% of predicted value	Discontinue bleomycin

If suspected bleomycin induced pneumonitis, seek respiratory opinion and consider antibiotics (as per local policy) and prednisolone (1mg/kg/day).

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Cardiotoxicity
Pulmonary fibrosis
Neurotoxicity
Cardiotoxicity, arrhythmias
post-therapy MDS

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Mucositis
Fatigue
Constipation
Dyspepsia
Hyperglycaemia
Alopecia

- **Other side effects**

Rash

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.

Procarbazine:
Alcohol: Procarbazine has a weak disulfiram-like effect and can lead to alcohol intolerance.
MAO inhibition: Procarbazine is a weak inhibitor of MAO and can cause CNS side-effects. Care should be taken when co-prescribing antihypertensives, CNS depressants or tricyclic antidepressants.
Barbiturates: Barbiturates can cause increased CNS depression with procarbazine.

Vinblastine:
Erythromycin: may increase vinblastine toxicity.

Additional comments
Patients requiring blood transfusion will require irradiated blood products indefinitely.

References

- Proctor SJ, et al. Evaluation of treatment outcome in 175 patients with Hodgkin lymphoma aged 60 years or over: the SHIELD study. Blood. 2012 Jun 21; 119(25):6005-15.
- A. Levis, et al VEPEMB in elderly Hodgkin's lymphoma patients Annals of Oncology. 2004; 15:123–128.
- BCSH Guidelines for the First Line Management of Classical Hodgkin Lymphoma. Final Version Feb 2014. Accessed 09 March 2015.

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