BEACOPP-14/ Escalated BEACOPP

Indication

Advanced stage Hodgkin Lymphoma where escalated therapy is indicated.

Early Stage Classical Hodgkin Lymphoma with positive interim PET-CT (Deauville 3 or more).

Patients must have WHO performance status 0-2, be aged ≤ 60 years with adequate cardiac function (e.g. LVEF > 50%) and adequate pulmonary function (e.g. transfer factor [TLCO/KCO] within 25% of normal predicted value).

Treatment should be discussed and agreed at a lymphoma MDT prior to initiation.

ICD-10

Codes with a prefix C81.

Regimen details

BEACOPP 14:

Day	Drug	Dose	Route
1	Doxorubicin	25mg/m^2	IV bolus
1	Cyclophosphamide	650mg/m^2	IV bolus
1 to 3	Etoposide	100mg/m^2	IV infusion
1 to 7	Procarbazine	100mg/m^2 (to nearest 50mg)	PO
1 to 7	Prednisolone	80mg/m^2	PO
8	Vincristine	1.4mg/m^2 (max 2mg)	IV infusion
8	Bleomycin	10,000units/m^2	IV infusion
9 to 13	G-CSF (as per local policy)		SC

Escalated BEACOPP:

Day	Drug	Dose	Route
1	Doxorubicin	35mg/m^2	IV bolus
1	Mesna	1000mg/m^2 prior to cyclophosphamide	IV infusion
1	Cyclophosphamide	1250mg/m^2	IV infusion
1	Mesna	1000mg/m^2 4 hours post cyclophosphamide	IV infusion
1 to 3	Etoposide	200mg/m^2	IV infusion
1 to 7	Procarbazine	100mg/m^2 (to nearest 50mg)	PO
1 to 14	Prednisolone	40mg/m^2	PO
8	Vincristine	1.4mg/m^2 (max 2mg)	IV infusion
8	Bleomycin	10,000units/m^2	IV infusion
9 to 13	G-CSF (as per local policy)		SC

If bulky disease consider pre-hydration with 0.9% sodium chloride over 4-6 hours. Assess risk of tumour lysis syndrome. Patients should drink 3L of fluid on the day of cyclophosphamide treatment.

Cycle frequency

BEACOPP 14: 14 days
Escalated BEACOPP: 21 days

Number of cycles

BEACOPP 14: Up to 8 cycles (see below).
Escalated BEACOPP: Up to 6 cycles.

In advanced stage disease, when used after ABVD with a positive interim PET-CT (PET2), a further PET-CT is advised after 4 cycles of BEACOPP 14 or 3 cycles of escalated BEACOPP. If the further PET-CT (PET3) is negative recommend a further 2 cycles of BEACOPP14 or 1 cycle of escalated BEACOPP. Optimal timing for interim PET-CT is day 12 (day 9-13) from the start of a cycle.
Escalated BEACOPP may be used as first line therapy for advanced Hodgkin lymphoma and 6 cycles given when interim PET scan is not recommended, however one should be carried out at the end of the treatment to assess the need for radiotherapy.

Alternatively escalated BEACOPP may be given for two cycles then PET-CT performed to assess response with PET negative cases treated to a total of 4 cycles and PET positive to 6 cycles with end of therapy PET-CT to assess the need for radiotherapy.

Administration

Consider placement of a PICC or central line.

Doxorubicin is administered by slow IV bolus into the arm of a fast running drip of sodium chloride 0.9%.

Mesna is administered in 100mL sodium chloride 0.9% over 15 minutes. The first dose is given prior to cyclophosphamide and a second dose is given 4 hours after the cyclophosphamide.

Cyclophosphamide is administered as an IV bolus or as an IV infusion in 250-500mL sodium chloride 0.9% over 30 minutes.

Etoposide is administered in 1000mL-2000mL (concentration dependent) sodium chloride 0.9% over 60 minutes.

Procarbazine is available as 50mg capsules. Capsules should be swallowed whole with a glass of water.

Prednisolone is available as 5mg and 25mg tablets. The dose should be taken each morning with or after food.

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

Bleomycin is administered in 100mL sodium chloride 0.9% over 30 minutes.

Pre-medication

Hydrocortisone 100mg IV prior to each bleomycin dose.

Emetogenicity

This regimen has high emetic potential on day 1, moderate emetic potential on days 2-7 and mild emetic potential on day 8.

Additional supportive medication

Allopurinol 300mg OD (or 100mg OD if creatinine clearance <20mL/min) for the first cycle.
H_2 antagonist or proton-pump inhibitor as per local policy.
Antiemetics as per local policy.
Mouth care as per local policy.
PCP prophylaxis e.g. co-trimoxazole as per local policy to continue until 6 months after treatment stops.

Antiviral prophylaxis
Antifungal (fluconazole) and antibiotic cover (ciprofloxacin) as per local policy may be appropriate during periods while neutrophils < 0.5 x10^9/L.

Extravasation

Vincristine and doxorubicin are vesicant (group 5).
Cyclophosphamide and bleomycin neutral (group 1).
Etoposide is an irritant (group 3).

Investigations – pre first cycle

Investigation	Validity period
FBC	7 days
U+Es (including creatinine)	7 days
LFTs	7 days
Calcium	7 days
Magnesium	7 days
Pulmonary Functions Tests (including transfer factor)	28 days

Hepatitis B core antibody and hepatitis BsAg, hepatitis C antibody, HIV 1+2 serology must be tested prior to commencing treatment.

ECG and consider echocardiogram if cardiac history. Patients with significant history of ischaemic heart disease or hypertension must have an acceptable LVEF ≥ 50%.

Prior to commencing treatment with unmodified drug doses patients must meet the following parameters, however first cycle doses are usually not modified for cytopenias:

Investigation	Limit
Neutrophils *	≥ 1.5 x 10^9/L
Platelets*	≥ 100 x 10^9/L
Calculated CrCl	≥ 60ml/min
Bilirubin	≤ 1.0 x ULN
ALT/AST	≤ 1.0 x ULN

* unless due to bone marrow infiltration

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	72 hours and prior to day 8
U+E (including creatinine)	72 hours and prior to day 8
LFTS	72 hours and prior to day 8

Standard limits in subsequent cycles for day 1 administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	Limit
WBC	≥ 2.5 x 10^9/L
Platelets	≥ 80 x 10^9/L
Calculated CrCl	≥ 60mL/min
Bilirubin	≤ 1.0 x ULN
ALT/AST	≤ 1.0 x ULN

Dose modifications

- ### Haematological toxicity

BEACOPP 14

Day 1:

Cycle 1: proceed with full dose therapy, particularly when there are known lymphoma infiltrates in the marrow.

Cycle 2 onwards:

WBC ($x10^9$/L)		**Platelets** ($x10^9$/L)	**Dose modification**
≥ 2.5	and	≥ 80	100% doses
< 2.5	or	< 80	Delay 1 week or until recovery Adjust dose as per table below

Delay in white cell count or platelet recovery	**Dose modification**
< 1 week	Once counts recovered continue with 100% doses
1-2 weeks	Once counts recovered 75% doses of cyclophosphamide, doxorubicin, etoposide and procarbazine
> 2 weeks	Once counts recovered 50% doses of cyclophosphamide, doxorubicin, etoposide and procarbazine

Day 8 drugs should be given on schedule and dose irrespective of FBC.

Escalated BEACOPP:

Day 1:

Cycle 1: proceed with full dose therapy, particularly when there are known lymphoma infiltrates in the marrow.

Cycle 2 onwards: If WBC ≥ 2.5 $x10^9$/L and platelets > 80 $x10^9$/L treatment should continue with 100% doses. Doses should be reduced as per the table below if any of the following occur:

- Grade 4 leucopenia (WBC < 1.0 $x10^9$/L) for more than 4 days
- Grade 4 thrombocytopenia (platelets < 25 $x10^9$/L)
- Grade 4 infection
- Grade 4 mucositis
- Any adverse event that required a 2 week treatment delay

After each of these adverse events the doses of cyclophosphamide and etopside should be reduced by one level from escalated to standard doses on the scale in the table below:

Drug	**Level 1- escalated**	**Level 2**	**Level 3**	**Level 4**	**Level 5 – standard**
Cyclophosphamide	1250mg/m^2	1100 mg/m^2	950 mg/m^2	800 mg/m^2	650 mg/m^2
Etoposide	200 mg/m^2	175 mg/m^2	150 mg/m^2	125 mg/m^2	100 mg/m^2

If adverse effects occur in 2 successive cycles, standard doses (i.e. level 5) should be used for all subsequent doses.

Day 8 drugs should be given on schedule and dose irrespective of FBC findings.

- ### Renal impairment

Creatinine clearance (mL/min)	**Cyclophosphamide dose**	**Bleomycin dose**
≥ 50	100%	100%
10-50	75%	75%
< 10	50%	50% - discuss with consultant

Creatinine clearance (mL/min)	Etoposide dose
≥ 60	100%
30-59	85%
15-29	75%
< 15	Consider 50% - discuss with consultant

Doxorubicin - no dose adjustment required, consultant decision if severe renal impairment.

Procarbazine - if CrCl 30-45 mL/min consider 50% dose, if < 30mL/min consultant decision whether to discontinue.

Vincristine - consultant decision if CrCl < 30mL/min.

- **Hepatic impairment**

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Doxorubicin dose**
≤ 1.0	and	< 2 x ULN	100%
> 1.0 - 2.5	or	2-3 x ULN	50%
> 2.5 - 4.0			25%
> 4.0			Omit

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Etoposide dose**	**Vincristine dose**
≤ 1.25	and	< 1.0	100%	100%
> 1.25 - 2.5	or	> 1.0 - 3.0	50%	50%
> 2.5	or	> 3.0	Discuss with consultant - consider 25% or omit	Consider omitting

Bilirubin (x ULN)	**Procarbazine dose**
≤ 2.0	100%
> 2.0	50%
> 5.0 or AST/ALT > 3.5 ULN	Consider omission (discuss with consultant)

Cyclophosphamide – if bilirubin > 2.5 x ULN consider dose reduction consultant decision
Bleomycin - No specific advice regarding use in hepatic impairment, consultant decision.

Other toxicities

For patients who develop ≥ grade 3 ileus, delay treatment until ≤ grade 1 and then continue with 75% vincristine. If ≥ grade 3 ileus recurs, vincristine should be discontinued.

Neurotoxicity

Toxicity	Definition	Dose adjustment
Neuropathy	Grade 2 (moderate symptoms)	Consider reducing procarbazine to 75% or/and Reduce vincristine to 50%
	Grade 3+ (severe symptoms, limiting self-care)	Discontinue treatment

Pulmonary toxicity

All patients reporting cough or shortness of breath should have a chest X-ray and pulmonary function tests prior to administration of bleomycin. Bleomycin should be discontinued if any clinical signs or CXR evidence of pulmonary infiltration/fibrosis develop, or if the transfer factor is <50% of the predicted value.

Pulmonary fibrosis is a greater risk in smokers, prior radiation to the thorax, the elderly and a cumulative dose > 400,000IU.

High concentrations of oxygen (>30%) should be avoided unless absolutely necessary. Patients should be warned that if they have future general anaesthetics they must inform the anaesthetist that they have received bleomycin. They should be advised against scuba diving.

Cardiac toxicity

Further doxorubicin is contraindicated in patients already treated with the maximum cumulative dose of doxorubicin of 450mg/m^2 or other anthracyclines.
Patients with a baseline ejection fraction < 50%, consider withholding doxorubicin / monitoring cardiac function; if, > 20% reduction on repeat ECHO they should not receive further anthracyclines.

Skin toxicity

Particularly of the hands and feet is seen with bleomycin. Bleomycin should be discontinued only if it restricts activity.

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

- **Serious side effects**

Treatment-related mortality (4-5%)
Myelosuppression
Cardiotoxicity
Pulmonary fibrosis
Aseptic osteonecrosis of the hip
Myelodysplastic syndrome and AML, secondary malignancy
Infertility
Anaphylaxis

- **Frequently occurring side effects**

Insomnia
Alopecia
Ovarian failure, amenorrhoea, sterility,
Nausea and vomiting
Stomatitis, ulceration,
Diarrhoea, constipation
Abdominal pain
Mucositis

- **Other side effects**

Discolouration of urine, haemorrhagic cystitis
CNS depression
Rash
Muscle weakness
Respiratory: tachypnoea, rales, acute or chronic interstitial pneumonitis and pulmonary fibrosis
Nasal congestion, epistaxis

Significant drug interactions – for full details consult product literature/ reference texts

Coumarin-derived anticoagulants such as warfarin: patients established on warfarin should either be changed to low molecular weight heparin or have weekly monitoring of INR. Patients who are initiated on anti-coagulation should remain on low molecular weight heparin until completion of the course of chemotherapy.
Phenytoin and fosphenytoin: close monitoring and/or alternative agents are recommended if co-prescribed with this regimen. Phenytoin serum levels may be decreased, possibly as a result of decreased absorption and/or increased metabolism.

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. Interactions with tyramine-containing foodstuffs must be borne in mind.
Barbiturates: Phenobarbital can lead to a reduced anti-tumour effect of lomustine due to induction of hepatic enzymes and increased elimination. Barbiturates can cause increased CNS depression with procarbazine.

Vincristine
Avoid itraconazole, voriconazole or posaconazole within a week of treatment because of increased risk of neuropathy with co-administration.

Additional comments

Encourage patients who smoke to stop – offer referral to smoking cessation services.

Cardiotoxicity has been associated with anthracyclines, with adverse events being more common in patients with a prior history of coronary artery disease. Caution must be taken in patients with a history of significant cardiac disease, arrhythmias or angina pectoris.

Doxorubicin has a life time maximum cumulative dose of 450mg/m^2, less if prior/other anthracycline exposure.

References

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