LACE high dose therapy with autologous stem cell support

Indication

Aggressive non-Hodgkin lymphoma: patients failing first line therapy (primary refractory or relapsed) and chemosensitive to salvage therapy

Hodgkin lymphoma: patients failing first line therapy (primary refractory or relapsed) and chemosensitive to salvage therapy

Indolent non-Hodgkin lymphoma: relapsed (any number of relapses) and responsive to salvage chemotherapy.

Patients must have had an adequate peripheral blood stem cell collection before consideration for high dose chemotherapy and be passed as medically fit for high dose therapy.

Regimen details

Day	Drug	Dose	Route
-7	Lomustine	200mg/m^2 single dose rounded to nearest 40mg	PO
-7 to -5	Etoposide	330mg/m^2 once daily	IV infusion
-6 to -5	Cytarabine	2 grams/m^2 once daily	IV infusion
-4 to -2	Mesna	3600mg/m^2 once daily	IV infusion
-4 to -2	Cyclophosphamide*	1800mg/m^2 once daily	IV infusion
0	Re-infusion of stem cells	At least 2x 10^6 CD34+ cells / kg body weight	IV infusion

*Hydration required (see below)

Cycle frequency

N/A

Administration

Lomustine is available as 40mg capsules. Lomustine capsules should be swallowed whole with water.

Etoposide is administered in sodium chloride 0.9% (concentration dependent) and infused over 2 hours. Consider using etoposide phosphate (Etopophos) due to high dose and therefore high volume of fluid required.

Cytarabine is administered in 1 litre sodium chloride 0.9% and infused over 2 hours.

Mesna is administered in 1 litre of sodium chloride 0.9% and infused over 24 hours with the first dose starting at the same time as the first dose of cyclophosphamide on day -4.

Cyclophosphamide is administered in 500ml sodium chloride 0.9% and infused over 1 hour.

Hydration

Hydration is indicated on the days of cyclophosphamide to reduce the risk of haemorrhagic cystitis as per local policy. (e.g. total of at least 3 litres over 24 hours including chemotherapy drug volumes). Urine should be tested for haematuria at baseline and then at least every 6 hours. A strict fluid balance should be maintained.

Time	Drug	Infusion fluid and volume	Additives	Rate/infusion time	Notes
0 hrs	Cyclophosphamide	Sodium Chloride 0.9% 500ml	-	Infuse over 1 hr at 500ml/hr	Run concurrently with mesna
0 hrs	Mesna	Sodium Chloride 0.9% 1000ml	-	Infuse over 24hrs at 42ml/hr	Run concurrently with cyclophosphamide
0 hrs	Hydration	Glucose 2.5%/ Sodium Chloride 0.45% 1000ml	Potassium Chloride 20mmol per 1000ml	Infuse at 62.5ml/hr continuously until 24hrs after last dose of cyclophosphamide. DISCARD ANY REMAINING FLUID.	Start at the same time as cyclophosphamide/ mesna

Pre-medication
Antiemetics as per local guidelines

Emetogenicity
This regimen has high emetic potential.

Additional supportive medication
Allopurinol 300mg OD for patients in a partial remission (100mg OD if CrCl<20ml/min).
Prednisolone 0.5% eye drops 1 drop both eyes QDS from day -6 until day zero inclusive (5 days after last dose of cytarabine).
H_2 antagonist or proton pump inhibitor if required.
Mouthwashes as per local policy.
Anti-emetics as per local policy.
GCSF as per local policy.
Antifungal and antiviral prophylaxis as per local policy.
Prophylactic antibiotics as per local policy.
PCP prophylaxis as per local policy.

Extravasation
Etoposide is irritant (Group 3)
Etoposide phosphate (Etopophos) is an inflammatant (Group 2)
Cytarabine and cyclophosphamide are neutral (Group 1)

Investigations

Investigation	**Validity period** (or as per local policy)
FBC	7 days
U+Es (including creatinine)	7 days
LFTs	7 days
Pulmonary Functions Tests (including transfer factor)	28 days
Chest X ray	28 days
Echocardiogram	28 days

Other pre-treatment investigations:
Full medical work-up and assessment
ECG
Dental review
Chest/Sinus CT
Virology screen

Standard limits for administration to go ahead

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

Investigation	**Limit**
Calculated CrCl	> 60ml/min
Bilirubin	< 1.2 x ULN
AST/ALT	< 1.5 x ULN

Before proceeding the patient's consultant must be satisfied that the patient has adequate cardiac and pulmonary function.

Dose modifications

- **Renal impairment**

Discuss dose changes with the patient's consultant

CrCl (mL/min)	**Lomustine dose**	**Cytarabine dose**
≥ 60	100%	100%
45-59	75%	60%
30-44	50%	50%
<30	Not recommended- consultant decision	Contraindicated- consultant decision

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

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

- **Hepatic impairment**

Discuss dose changes with the patient's consultant. High dose chemotherapy would not normally be appropriate for patients with significant hepatic impairment.

Bilirubin (x ULN		**AST/ALT**	**Etoposide dose**
< 1.5	and	< 2 x ULN	100%
1.5-3	or	2 – 5 x ULN	50%
> 3	or	> 5 x ULN	Consultant decision

Lomustine – Lack of information. Consultant decision

Cyclophosphamide - Reduced activation of pro-drug in severe hepatic impairment, however high dose therapy unlikely to be appropriate in this scenario.

Cytarabine - dose should be reduced to 50% if bilirubin >1.5xULN.

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

- **Serious side effects**
  Death
  Severe myelosuppression
  Severe stomatitis/mucositis
  Hypersensitivity and allergic reaction
  Haemorrhagic cystitis (cyclophosphamide)
  CNS toxicity (cytarabine)
  Secondary malignancy
  Peripheral neuropathy
  Pulmonary toxicity
  Cardiotoxicity
  Hepatotoxicity

- **Frequently occurring side effects**
  Nausea and vomiting
  Myelosuppression
  Fatigue, flu-like symptoms
  Anorexia, weight loss
  Constipation
  Diarrhoea
  Alopecia
  Conjunctivitis (cytarabine)
  Haemorrhagic cystitis (cyclophosphamide)

- **Other side effects**
  Metallic taste
  Nasal congestion
  Hyperbilirubinaemia and elevated transaminases
  Rash
  Xerostomia/parotitis

Significant drug interactions – this is not an exhaustive list, for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Switch patient to a low molecular weight heparin during treatment

Lomustine:
Clozapine: increased risk of agranulocytosis - avoid concomitant use
Phenobarbital: Increased metabolism of lomustine - avoid concomitant use

Etoposide:
Ciclosporin: High dose ciclosporin markedly increases etoposide levels
Enzyme inducing antiepileptics: Metabolism of etoposide may be increased by phenytoin, phenobarbital and possibly carbamazepine
Phenylbutazone, sodium salicylate and salicylic acid: can affect protein binding of etoposide.

Cytarabine:
Clozapine: increased risk of agranulocytosis- avoid concomitant use
Digoxin: cytarabine may affect plasma digoxin levels- consider monitoring

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 possibly- avoid
Itraconazole: may increase adverse effects of cyclophosphamide – avoid itraconazole until 24 hrs after last cyclophosphamide dose
Phenytoin: Phenytoin absorption may be reduced by cyclophosphamide- monitor levels. Cyclophosphamide metabolism may be affected by phenytoin although clinical relevance unclear.
Grapefruit juice: decreased or delayed activation of cyclophosphamide. Patients should be advised to avoid grapefruit juice for 48 hours before and on the day of cyclophosphamide.

Additional comments

Irradiated blood products required to prevent rare occurrence of transfusion-associated graft versus host disease. The patient should be provided with Department of Health irradiated blood product information sheet and card

References

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- Summary of Product Characteristics Lomustine (Medac) accessed via www.medicines.org.uk (08/06/2016)
- Summary of Product Characteristics Etoposide (Accord) accessed via www.medicines.org.uk (08/06/2016)
- Summary of Product Characteristics Cytarabine (Hospira) accessed via www.medicines.org.uk (08/06/2016)
- Summary of Product Characteristics Cyclophosphamide (Sandoz) accessed via www.medicines.org.uk (08/06/2016)
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- University College London Hospitals. Dosage Adjustment for Cytotoxics in Hepatic Impairment. Version 3, updated January 2009.

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