ETOPOSIDE/DEXAMETHASONE - HLH

INDICATION

Haemophagocytic Lymphohistiocytosis, in the absence of a rheumatologic/infective disorder driving a macrophage activation syndrome.

An alternative protocol exists for the treatment of HLH involving the use of Anakinra by rheumatologists.

TREATMENT INTENT

Disease control, with a view to discover underlying driver (often lymphoma).

It is very unusual for genetic causes of HLH (primary HLH) to present in adulthood. For primary HLH, this protocol is used initially for control, then as a bridge to allogeneic transplantation (HSCT). Close liaison with the immunology, infectious disease and rheumatology teams as appropriate.

PRE-ASSESSMENT

1. Blood tests - FBC, reticulocytes, ferritin, coagulation screen (incl. PT, APTT, fibrinogen), DAT, U&Es, LDH, ESR, urate, calcium, magnesium, creatinine, serum bicarbonate, LFTs, albumin, glucose, fasting triglycerides, Igs, β_2 microglobulin, soluble IL-2 receptor (sCD25) and soluble CD163 if available.
2. A work-up for infectious causes including blood cultures, urinalysis, urine cultures, thin and thick blood smear, purified protein derivative (or T-spot), viral titres, and serology (Hep A, Hep B core antibody and Hep BsAg, Hepatitis C antibody, EBV, CMV, HSV, VZV, HHV6+8, rubella, varicella virus, parvovirus, adenovirus, torovirus, coxsackie virus, influenza, parvovirus, adenovirus, measles virus, HIV 1+2, Leishmaniasis, brucellosis, tuberculosis, mycoplasma, syphilis, toxoplasmosis, Pneumocystis jiroveci, Candida spp.
3. Bone marrow aspirate (including TB culture) + Trephine. Lymph node core or excision biopsy if suspicion of lymphoma. Consider Liver biopsy. Perform ZN stain on lymph node and bone marrow biopsy to investigate tuberculosis.
4. Imaging as guided by clinical presentation – CXR, cross-sectional imaging to look for lymphoma, CNS imaging if clinical suspicion of CNS disease.
5. Lumbar puncture – cell and protein content (consider lactate and glucose); CSF cell morphological and immunological analyses
6. *Molecular diagnostics to be sent on a case by case basis – eg perforin, Munc 13-4, Munc 18-2, Syntaxin 11. These tests should only be done if strong suspicion of underlying genetic drivers. Close liaison with immunology and molecular immunology lab at Great Ormond Street*
7. HLA-typing
8. Ensure histology is confirmed prior to administration of chemotherapy and document in notes
9. Urine pregnancy test - before cycle 1 of each new chemotherapy course in women of child-bearing age unless they are post-menopausal, have been sterilised or undergone a hysterectomy
10. ECG +/- Echo- *if clinically indicated.*

11. Record performance status (WHO/ECOG)
12. Record height and weight (also needed to calculate CrCl)
13. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment
14. Fertility - it is very important the patient understands the potential risk of infertility, all patients should be offered fertility advice by referring to the Oxford Fertility Unit
15. Consider dental assessment / advise dental check is carried out by patient's own dental practitioner before treatment starts
16. Treatment should be agreed in the relevant MDT
17. Complete history – Family history (consanguinity, previous childhood deaths in family or relatives, late miscarriages of the mother), recent infections, vaccinations, malignancy, underlying immune disorders, pharmacological immunosuppression, rheumatological conditions, family history and previous bouts of similar symptoms, fever (duration and level), neurological symptoms (incl. irritability, ataxia, convulsions, others), oedema, jaundice, skin rash
18. Cardiopulmonary examination
19. Evaluation for hepatosplenomegaly, lymphadenopathy, rashes, neurological abnormalities (incl. cranial nerve abnormalities and cerebellar dysfunction), evidence of bleeding or bruising, temperature, jaundice, oedema, tonsillitis, dyspnoea, tachypnoea, ascites, blood pressure, neurological examination

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DRUG REGIMEN / CYCLE FREQUENCY

INITIAL THERAPY

Weeks	DEXAMETHASONE	ETOPOSIDE
1 - 2	**10 mg/m^2 PO** once daily (IV if PO not tolerated)	**150 mg/m^2** in 1000mL 0.9% sodium chloride IV infusion over 2 hours **TWICE** weekly
3 - 4	**5 mg/m^2 PO** once daily (IV if PO not tolerated)	**150 mg/m^2** in 1000mL 0.9% sodium chloride IV infusion over 2 hours **ONCE** weekly
5 - 6	**2.5 mg/m^2 PO** once daily (IV if PO not tolerated)	
7	**1.25 mg/m^2 PO** once daily (IV if PO not tolerated)	
8	Taper & discontinue	

Dexamethasone is dosed using 2mg and/or 0.5mg strength tablets.**INTRATHECAL THERAPY**
The CSF is evaluated at diagnosis and after 2 weeks. If after 2 weeks there is clinical evidence of progressive neurological symptoms or if an abnormal CSF (cell count and protein) has not improved, additional CNS therapy is initiated.

Weeks	METHOTREXATE INTRATHECAL
3 – 6	12 mg **ONCE** weekly

CONTINUATION THERAPY

Weeks	DEXAMETHASONE and ETOPOSIDE (given on alternate weeks)	
9 - 52	ODD number weeks	**DEXAMETHASONE 10 mg/m^2 PO** once daily for 3 days
	EVEN number weeks	**ETOPOSIDE 150 mg/m^2** in 1000mL 0.9% sodium chloride IV infusion over 2 hours **ONCE** weekly

CICLOSPORIN 3 mg/kg PO BD: Starting at week 9. Measure baseline renal function and monitor. Aim for Ciclosporin levels of 200 mcg/L. Consider tacrolimus as alternative if not tolerated (discuss with consultant).

Length of continuation therapy

Proceed to HSCT or other definitive treatment as quickly as possible because of the ongoing risks of infection, disease reactivation, or leukemia/MDS related to prolonged use of etoposide. Thereafter, and for **Reactivation** or **Salvage** therapy, discuss with consultant.

IF AN UNDERLYING HAEMATOLOGICAL MALIGNANCY IS FOUND, DIRECTED TREATMENT (IDEALLY CONTAINING ETOPOSIDE) SHOULD BE INITIATED IMMEDIATELY.

RESTAGING

Continuation criteria at 2 and 4 weeks:

- No fever
- Reduction of spleen size
- Platelets ≥ 100 x 10^9/L
- Normal fibrinogen
- Decreasing ferritin levels (by 25%)

Continuation criteria after 8 weeks:

- No fever
- No splenomegaly (isolated moderate splenomegaly may persist in some patients)
- No cytopenia (Hb ≥ 90g/L, Platelets ≥ 100 x 10^9/L, ANC ≥ 0.5 x 10^9/L)
- No hypertriglyceridaemia (<3 mmol/L / <265 mg/dL)
- No hyperferritinaemia ≥ 500microgram/L
- Normal CSF (for previously CSF positive patients)
- Decrease in sCD25 if available

DOSE MODIFICATIONS

Haematological

Weeks	Haematological parameters	Dose modification
1-2	Generally no dose reduction recommended, irrespective of marrow cellularity	
Other	Bone marrow toxicity	Discuss with Consultant

Non- Haematological toxicity

Toxicity	Modification
Grade 3 or above nephrotoxicity related to Ciclosporin	Review ciclosporin dose Consider switching to tacrolimus
Grade 2 or above neurotoxicity	Discuss with consultant

Etoposide

Renal impairment	Hepatic impairment
GFR (mL/min) Dose > 50 100% 15-50 75% < 15 50% Subsequent doses should be based on clinical response. **Dialysis** Start at reduced dose and increase according to clinical response.	Bilirubin 26-51 micromol/L or AST 60-180u/L - give 50% of the dose Bilirubin > 51 micromol/L or AST > 180u/L - clinical decision, consider giving 25% of the dose, or omit.

CONTRAINDICATIONS

Hypersensitivity to the active substance or excipients, or

DEXAMETHASONE Systemic infection (unless antimicrobials given).
ETOPOSIDE Hypersensitivity to also podophyllotoxines or podophyllotoxine-derivatives, severe liver impairment, severe myelosuppression or breastfeeding.

SPECIAL WARNINGS / PRECAUTIONS / MONITORING

DEXAMETHASONE Adrenal suppression after abrupt withdrawal after prolonged therapy, infections with prolonged courses, adrenal insufficiency.
ETOPOSIDE Possible anaphylactic reaction manifested as chills, fever, flushing, tachycardia, bronchospasm, dyspnoea and hypotension.
Avoid concomitant use of live vaccines in immunosuppressed patients.

CONCURRENT MEDICATION

Broad spectrum antibiotics	As guided by clinical presentation
CO-TRIMOXAZOLE	480 mg PO once daily on Mondays, Wednesdays and Fridays. Continue for 3 months after treatment. Consider reducing to 480mg PO twice weekly during neutropenic periods.
Antifungal prophylaxis	As per local formulary for high risk prophylaxis.
ACICLOVIR	200 mg PO three times a day for duration of treatment and for 3 months after completion.
Proton pump inhibitor (PPI)	Daily for the duration of treatment,
IVIG	Consider IVIG, during initial and continuation therapy. Prior approval from local Immunoglobulin assessment panel required.
RITUXIMAB	In proven EBV associated HLH. IV 375mg/m^2 given weekly for 4 doses
CICLOSPORIN	Start at 3mg/kg BD PO from week 9, as soon as a clinical response has been achieved from initial therapy. Monitor level weekly initially.

ANTI-EMETICS

Low emesis risk

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Very commonly reported:

DEXAMETHASONE Adverse glucocorticoid effects, increased risk of infection, changes / increases in blood sugar levels (high dose or long term treatment), changes in mood and behaviour, psychiatric disorders, irritability, insomnia, headaches, dizziness, cataracts, bone thinning (long-term use), increased appetite, fluid retention, heartburn, indigestion, muscle weakness, impaired wound healing
ETOPOSIDE Myelosuppression, abdominal pain, constipation, nausea and vomiting, anorexia, hepatotoxicity, alopecia, pigmentation, asthenia, malaise, hypotension and bronchospasm, mutagenicity, carcinogenicity. Elevated risk of toxicity with a lower serum albumin level.

EXTRAVASATION RISK

Etoposide: irritant

TREATMENT RELATED MORTALITY

High mortality on treatment usually due to underlying disease.

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